

AO

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
28 June 2001 (28.06.2001)

PCT

(10) International Publication Number
WO 01/46195 A1

(51) International Patent Classification: C07D 487/04,
A61K 31/435, 31/415, A61P 25/28, 27/00, 17/14

(21) International Application Number: PCT/US00/30436

(22) International Filing Date:
6 November 2000 (06.11.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/171,391 21 December 1999 (21.12.1999) US

(71) Applicant: GPI NIL HOLDINGS, INC. [US/US]; 222
Delaware Avenue, Wilmington, DE 19801 (US).

(74) Agent: NATH, Gary, M.; Nath & Associates PLLC, 1030
15th Street, N.W., 6th Floor, Washington, DC 20005-1503
(US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(82) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— With international search report.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 01/46195 A1

(54) Title: HYDANTOIN DERIVATIVE COMPOUNDS, PHARMACEUTICAL COMPOSITIONS, AND METHODS OF USING SAME

(57) Abstract: The present invention relates generally to novel hydantoin derivative compounds, pharmaceutical compositions containing such compounds, and methods for their use in preventing and/or treating neurological disorders, including physically damaged nerves and neurodegenerative diseases; for treating alopecia and promoting hair growth; for treating vision disorders and/or improving vision; for treating memory impairment and/or enhancing memory performance; and for treating sensorineural hearing loss by administering such compounds.

- 1 -

HYDANTOIN DERIVATIVE COMPOUNDS, PHARMACEUTICAL
COMPOSITIONS, AND METHODS OF USING SAME

BACKGROUND OF THE INVENTION

5

Field of Invention

This invention relates to novel hydantoin and hydantoin derivative compounds, their inclusion in pharmaceutical compositions, and their preparation and use for preventing and/or treating neurological disorders; for treating alopecia and promoting hair growth; for treating vision disorders and/or improving vision; for treating memory impairment and/or enhancing memory performance; and for preventing and/or treating hearing loss in an animal.

15

Description of Related Art

It has been found that picomolar concentrations of an immunosuppressant such as FK506 and rapamycin stimulate neurite outgrowth in PC12 cells and sensory nervous, namely dorsal root ganglion cells (DRGs). Lyons et al., *Proc. Of Natl. Acad. Sci.*, 1994 vol. 91, pp. 3191-3195. In whole animal experiments, FK506 has been shown to stimulate nerve regeneration following facial nerve injury and results in functional recovery in animals with sciatic nerve lesions.

Several neurotrophic factors effecting specific neuronal populations in the central nervous system have been identified. For example, it has been hypothesized that Alzheimer's disease results from a decrease or loss of nerve growth factor (NGF). It has thus been proposed to treat Alzheimer's patients with exogenous nerve growth factor or other neurotrophic proteins such as brain derived nerve factor (BDNF), glial derived nerve factor, ciliary neurotrophic factor, and neurotrophin-3 to increase the survival of degenerating neuronal populations.

Clinical application of these proteins in various neurological disease states is hampered by difficulties in the delivery and bioavailability of large proteins to

- 2 -

nervous system targets. By contrast, immunosuppressant drugs with neurotrophic activity are relatively small and display excellent bioavailability and specificity. However, when administered chronically, immunosuppressants exhibit a number of potentially serious side effects including nephrotoxicity, such as impairment of glomerular filtration and irreversible interstitial fibrosis (Kopp et al., 1991, *J. Am. Soc. Nephrol.* 1:162); neurological deficits, such as involuntary tremors, or non-specific cerebral angina such as non-localized headaches (De Groen et al., 1987, *N. Engl. J. Med.* 317:861); and vascular hypertension with complications resulting therefrom (Kahan et al., 1989 *N. Engl. J. Med.* 321: 1725).

Accordingly, there is a need for non-immunosuppressive, small-molecule compounds which are useful for neurotrophic effects and for treating neurodegenerative disorders.

Hair loss occurs in a variety of situations. These situations include male pattern alopecia, alopecia senilis, alopecia areata, diseases accompanied by basic skin lesions or tumors, and systematic disorders such as nutritional disorders and internal secretion disorders. The mechanisms causing hair loss are very complicated, but in some instances can be attributed to aging, genetic disposition, the activation of male hormones, the loss of blood supply to hair follicles, and scalp abnormalities.

The immunosuppressant drugs FK506, rapamycin and cyclosporin are well known as potent T-cell specific immunosuppressants, and are effective against graft rejection after organ transplantation. It has been reported that topical, but not oral, application of FK506 (Yamamoto et al., *J. Invest. Dermatol.*, 1994, 102, 160-164; Jiang et al., *J. Invest. Dermatol.* 1995, 104, 523-525) and cyclosporin (Iwabuchi et al., *J. Dermatol. Sci.* 1995, 9,

- 3 -

64-69) stimulates hair growth in a dose-dependent manner. One form of hair loss, alopecia areata, is known to be associated with autoimmune activities; hence, topically administered immunomodulatory compounds are expected to demonstrate efficacy for treating that type of hair loss. The hair growth stimulating effects of FK506 have been the subject of an international patent filing covering FK506 and structures related thereto for hair growth stimulation (Honbo et al., EP 0 423 714 A2). Honbo et al. discloses the use of relatively large tricyclic compounds, known for their immunosuppressive effects, as hair revitalizing agents.

The hair growth and revitalization effects of FK506 and related agents are disclosed in many U.S. patents (Goulet et al., U.S. Patent No. 5,258,389; Luly et al., U.S. Patent No. 5,457,111; Goulet et al., U.S. Patent No. 5,532,248; Goulet et al., U.S. Patent No. 5,189,042; and Ok et al., U.S. Patent No. 5,208,241; Rupprecht et al., U.S. Patent No. 5,284,840; Organ et al., U.S. Patent No. 5,284,877). These patents claim FK506 related compounds. Although they do not claim methods of hair revitalization, they disclose the known use of FK506 for effecting hair growth. Similar to FK506 (and the claimed variations in the Honbo et al. patent), the compounds claimed in these patents are relatively large. Further, the cited patents relate to immunomodulatory compounds for use in autoimmune related diseases, for which FK506's efficacy is well known.

Other U.S. patents disclose the use of cyclosporin and related compounds for hair revitalization (Hauer et al., U.S. Patent No. 5,342,625; Eberle, U.S. Patent No. 5,284,826; Hewitt et al., U.S. Patent No. 4,996,193). These patents also relate to compounds useful for treating autoimmune diseases and cite the known use of cyclosporin and related immunosuppressive compounds for hair growth.

However, immunosuppressive compounds by definition

- 4 -

suppress the immune system and also exhibit other toxic side effects. Accordingly, there is a need for non-immunosuppressive, small molecule compounds which are useful as hair revitalizing compounds.

5 The visual system is composed of the eyes, ocular adnexa and the visual pathways. Dysfunction of the visual system may lead to permanent or temporary visual impairment, i.e. a deviation from normal in one or more functions of the eye. Visual impairment manifests itself
10 in various ways and includes a broad range of visual dysfunctions and disturbances. Without limitation, these dysfunctions and disturbances include partial or total loss of vision, the need for correction of visual acuity for objects near and far, loss of visual field, impaired ocular
15 motility without diplopia (double vision), impaired or skewed color perception, limited adaptation to light and dark, diminished accommodation, metamorphopsic distortion, impaired binocular vision, paresis of accommodation, iridoplegia, entropion, ectropion, epiphora, lagophthalmos,
20 and scarring. See *Physicians' Desk Reference (PDR) for Ophthalmology*, 16th Edition, 6:47 (1988). The visual system may be adversely affected by various ophthalmologic disorders, diseases, injuries, and complications, including, without limitation, genetic disorders; disorders
25 associated with aging or degenerative diseases; disorders correlating to physical injury to the eye, head, or other parts of the body resulting from external forces; disorders resulting from environmental factors; disorders resulting from a broad range of diseases; and combinations of any of
30 the above.

The visual system is a complex system composed of numerous components. Visual impairment can involve the entire visual system, any one component, or any combination of components, depending upon the precise nature of the

- 5 -

circumstances. The eye is composed of a lens, which is suspended in the zonules of Zinn and is focused by the ciliary body. The ciliary body also secretes aqueous humor, which fills the posterior chamber, passes through the pupil into the anterior chamber, then drains primarily via the canal of Schlemm. The iris regulates the quantity of light entering the eye by adjusting the size of its central opening, the pupil. A visual image is focused onto the retina, the fovea centralis being the retinal area of sharpest visual acuity. The conjunctiva is the mucus membrane which lines the eyelids and the eyeball, and ends abruptly at the limbus conjunctivae, the edge of the conjunctiva overlapping the cornea. The cornea is the clear, transparent anterior portion of the fibrous coat of the eye; it is important in light refraction and is covered with an epithelium that differs in many respects from the conjunctival epithelium.

The retina is the innermost, light sensitive portion of the eye, containing two types of photoreceptors, cones, which are responsible for color vision in brighter light, and rods, which are essential for vision in dim light but do not perceive colors. After light passes through the cornea, lens system, and the vitreous humor, it enters the retina from the inside; that is, it passes through the ganglion cells and nerve fibers, the inner and outer plexiform layers, the inner and outer nuclear layers, and the internal and external limiting membranes before it finally reaches the layer of photoreceptors located near the outside of the retina, just inside the outermost pigment epithelium layer. The cells of the pigment epithelium layer act as an anatomical barrier to liquids and substances located outside of the eye, forming the "blood-retina" barrier, and provide nourishment, oxygen, a source of functionally useful substances like vitamin A, and phagocytosis of decomposition products to photoreceptor

- 6 -

cells. There is no anatomical connection between the pigment epithelium and the photoreceptor layer, permitting separation of the layers in some pathological situations.

When rods or cones are excited by light, signals are transmitted through successive neurons in the retina itself, into the optic nerve fibers, and ultimately to the cerebral cortex. Both rods and cones contain molecules that decompose on exposure to light and, in the process, excite the nerve fibers leading from the eye. The molecule in rods is rhodopsin. The three light-sensitive molecules in cones, collectively called iodopsin, have compositions only slightly different from that of rhodopsin and are maximally excited by red, blue, or green light, respectively.

Neither rods nor cones generate action potentials. Rather, the light-induced membrane hyperpolarization generated in the outer, photosensitive segment of a rod or cone cell is transmitted from the outer segment through the inner segment to the synaptic body by direct conduction of the electrical voltage itself, a process called electrotonic conduction. At the synaptic body, the membrane potential controls the release of an unknown transmitter molecule. In low light, rod and cone cell membranes are depolarized and the rate of transmitter release is greatest. Light-induced hyperpolarization causes a marked decrease in the release of transmitter molecules.

The transmitters released by rod and cone cells induce signals in the bipolar neurons and horizontal cells. The signals in both these cells are also transmitted by electrotonic conduction and not by action potential.

The rod bipolar neurons connect with as many as 50 rod cells, while the dwarf and diffuse bipolar cells connect with one or several cone cells. A depolarizing bipolar cell is stimulated when its connecting rods or cones are

- 7 -

exposed to light. The release of transmitter molecules inhibits the depolarizing bipolar cell. Therefore, in the dark, when the rods and cones are secreting large quantities of transmitter molecules, the depolarizing bipolar cells are inhibited. In the light, the decrease in release of transmitter molecules from the rods and cones reduces the inhibition of the bipolar cell, allowing it to become excited. In this manner, both positive and negative signals can be transmitted through different bipolar cells from the rods and cones to the amacrine and ganglion cells.

As their name suggests, horizontal cells project horizontally in the retina, where they may synapse with rods, cones, other horizontal cells, or a combination of cells types. The function of horizontal cells is unclear, although some mechanism in the convergence of photoreceptor signaling has been postulated.

All types of bipolar cells connect with ganglion cells, which are of two primary types. A-type ganglion cells predominately connect with rod bipolar cells, while B-type ganglion cells predominately connect with dwarf and diffuse bipolar cells. It appears that A-type ganglion cells are sensitive to contrast, light intensity, and perception of movement, while B-type ganglion cells appear more concerned with color vision and visual acuity.

Like horizontal cells, the Amacrine cells horizontally synapse with several to many other cells, in this case bipolar cells, ganglion cells, and other Amacrine cells. The function of Amacrine cells is also unclear.

The axons of ganglion cells carry signals into the nerve fiber layer of the eye, where the axons converge into fibers which further converge at the optic disc, where they exit the eye as the optic nerve. The ganglion cells transmit their signals through the optic nerve fibers to the brain in the form of action potentials. These cells, even when unstimulated, transmit continuous nerve impulses

- 8 -

at an average, baseline rate of about 5 per second. The visual signal is superimposed onto this baseline level of ganglion cell stimulation. It can be either an excitatory signal, with the number of impulses increasing above the baseline rate, or an inhibitory signal, with the number of
5 nerve impulses decreasing below the baseline rate.

As part of the central nervous system, the eye is in some ways an extension of the brain; as such, it has a limited capacity for regeneration. This limited
10 regeneration capacity further complicates the challenging task of improving vision, resolving dysfunction of the visual system, and/or treating or preventing ophthalmologic disorders. Many disorders of the eye, such as retinal photic injury, retinal ischemia-induced eye injury, age-
15 related macular degeneration, free radical-induced eye diseases, as well as numerous other disorders, are considered to be entirely untreatable. Other ophthalmologic disorders, e.g., disorders causing permanent visual impairment, are corrected only by the use of
20 ophthalmic devices and/or surgery, with varying degrees of success.

The immunosuppressant drugs FK506, rapamycin, and cyclosporin are well known as potent T-cell specific immunosuppressants, and are effective against autoimmunity,
25 transplant or graft rejection, inflammation, allergic responses, other autoimmune or immune-mediated diseases, and infectious diseases. It has been disclosed that application of Cyclosporin, FK-506, Rapamycin, Buspiron, Spiperone, and/or their derivatives are effective in
30 treating some ophthalmologic disorders of these types. Several ophthalmologic disorders or vision problems are known to be associated with autoimmune and immunologically-mediated activities; hence, immunomodulatory compounds are expected to demonstrate efficacy for treating those types
35 of ophthalmologic disorders or vision problems.

The effects of FK506, Rapamycin, and related agents in the treatment of ophthalmologic diseases are disclosed in several U.S. patents (Goulet et al., U.S. Patent No. 5,532,248; Mochizuki et al., U.S. Patent No. 5,514,686; 5 Luly et al., U.S. Patent No. 5,457,111; Russo et al., U.S. Patent No. 5,441,937; Kulkarni, U.S. Patent No. 5,387,589; Asakura et al., U.S. Patent No. 5,368,865; Goulet et al., U.S. Patent No. 5,258,389; Armistead et al., U.S. Patent No. 5,192,773; Goulet et al., U.S. Patent No. 5,189,042; 10 and Fehr, U.S. Patent No. 5,011,844). These patents claim FK506 or Rapamycin related compounds and disclose the known use of FK506 or Rapamycin related compounds in the treatment of ophthalmologic disorders in association with the known immunosuppressive effects of FK506 and Rapamycin. 15 The compounds disclosed in these patents are relatively large. Further, the cited patents relate to immunomodulatory compounds limited to treating autoimmunity or related diseases, or immunologically-mediated diseases, for which the efficacy of FK506 and Rapamycin is well 20 known.

Other U.S. patents disclose the use of cyclosporin, Spiperone, Buspirone, their derivatives, and other immunosuppressive compounds for use in the treatment of ophthalmologic diseases (Sharpe et al., U.S. Patent No. 25 5,703,088; Sharpe et al., U.S. Patent No. 5,693,645; Sullivan, U.S. Patent No. 5,688,765; Sullivan, U.S. Patent No. 5,620,921; Sharpe et al., U.S. Patent No. 5,574,041; Eberle, U.S. Patent No. 5,284,826; Sharpe et al., U.S. Patent No. 5,244,902; Chiou et al., U.S. Patent Nos. 30 5,198,454 and 5,194,434; and Kaswan, U.S. Patent No. 4,839,342). These patents also relate to compounds useful for treating autoimmune diseases and cite the known use of cyclosporin, Spiperone, Buspirone, their derivatives, and other immunosuppressive compounds in treating ocular 35 inflammation and other immunologically-mediated

- 10 -

ophthalmologic diseases.

The immunosuppressive compounds disclosed in the prior art suppress the immune system, by definition, and also exhibit other toxic side effects. Accordingly, there is
5 a need for non-immunosuppressant, small molecule compounds, and compositions and methods for use of such compounds, that are useful in improving vision; preventing, treating, and/or repairing visual impairment or dysfunction of the visual system; and preventing, treating, and/or resolving
10 ophthalmologic disorders.

There are also a number of patents on non-immunosuppressive compounds disclosing methods of use for permitting or promoting wound healing (whether from injury or surgery); controlling intraocular pressure (often
15 resulting from glaucoma); controlling neurodegenerative eye disorders, including damage or injury to retinal neurons, damage or injury to retinal ganglion cells, and macular degeneration; stimulating neurite outgrowth; preventing or reducing oxidative damage caused by free radicals; and
20 treating impaired oxygen and nutrient supply, as well as impaired waste product removal, resulting from low blood flow. These non-immunosuppressive substances fall into one of two general categories: naturally occurring molecules, such as proteins, glycoproteins, peptides, hormones, and
25 growth factors; and synthetic molecules.

Within the group of naturally occurring non-immunosuppressive molecules, several hormones, growth factors, and signaling molecules have been patented for use as supplements to naturally occurring quantities of such
30 molecules, as well as for targeting of specific cells where the particular molecule does not naturally occur in a mature individual. These patents generally claim methods of use for reducing or preventing the symptoms of ocular disease, or arresting or reversing vision loss.

35 Specifically, Louis et al., U.S. Patent Nos. 5,736,516

- 11 -

and 5,641,749, disclose the use of a glial cell line derived neurotrophic factor (GDNF) to stop or reverse the degeneration of retinal neurons (i.e. photoreceptors) and retinal ganglion cells caused by glaucoma, or other degenerative or traumatic retinal diseases or injuries. O'Brien, et al., U.S. Patent Nos. 5,714,459 and 5,700,909, disclose the use of a glycoprotein, Saposin, and its derivatives for stimulating neurite outgrowth and increasing myelination. To stop or reverse degeneration of retinal neurons, LaVail et al., U.S. Patent No. 5,667,968, discloses the use of a variety of neurotrophic proteins, including brain-derived neurotrophic factor, ciliary neurotrophic factor, neurotrophin-3 or neurotrophin-4, acidic or basic fibroblast growth factors, interleukin, tumor necrosis factor- α , insulin-like growth factor-2 and other growth factors. Wong et al., U.S. Patent No. 5,632,984, discloses the use of interferons, especially interferon α -2a, for treating the symptoms of macular degeneration by reducing hemorrhage and limiting neovascularization. Finally, Wallace et al., U.S. Patent No. 5,441,937, discloses the use of a lung-derived neurotrophic factor (NTF) to maintain the functionality of ciliary ganglion and parasympathetic neuron cells.

A key characteristic of factors derived from specific cell lines is their localization to specific cell lines or tissues; systemic treatment with these molecules would run a substantial risk of unintended, and potentially dangerous, effects in cell lines where the genes encoding these molecules are inactive. Similarly, hormones and growth factors often activate a large number of genes in many cell lines; again, non-localized application of these molecules would run a substantial risk of provoking an inappropriate, and potentially dangerous, response.

Within the category of synthetic molecules, most of the patented compounds are immunosuppressive and disclose

- 12 -

uses in treating inflammatory, autoimmune, and allergic responses, as discussed above. A few others are non-immunosuppressive and claim the ability to treat cellular degeneration, and in some cases promote cellular regeneration, most often in the context of their antioxidant properties.

Specifically, Tso et al., U.S. Patent No. 5,527,533, discloses the use of astaxanthin, a carotenoid antioxidant, for preventing or reducing photoreceptor damage resulting from the presence of free radicals. Similarly, Babcock et al., U.S. Patent No. 5,252,319, discloses the use of antioxidant aminosteroids for treating eye disease and injury, by increasing resistance to oxidative damage. Freeman, U.S. Patent No. 5,468,752, discloses the use of the antiviral phosphonylmethoxyalkylcytosines to reduce abnormally increased intraocular pressure.

Naturally occurring hormones, growth factors, cytokines, and signaling molecules are generally multifunctional and activate many genes in diverse cell lines. The present compounds do not, thus avoiding the unexpected, and potentially dangerous, side effects of systemic use. Similarly, the present compounds also avoid the potential unexpected side effects of introducing cell line-specific molecules into other cell lines where they do not naturally occur.

The epithelial hair cells in the organ of Corti of the inner ear, transduce sound into neural activity, which is transmitted along the cochlear division of the eighth cranial nerve. This nerve consists of fibers from three types of neurons (Spoendlin, H. H., in Friedmann, I. Ballantyne, J., eds. "Ultrastructural Atlas of the Inner Ear", London, Butterworth, pp. 133-164, (1984)) 1) afferent neurons, which lie in the spiral ganglion and connect the cochlea to the brainstem; 2) efferent olivocochlear neurons, which originate in the superior olivary complex;

- 13 -

and 3) autonomic adrenergic neurons, which originate in the cervical sympathetic trunk and innervate the cochlea. In the human, there are approximately 30,000 afferent cochlear neurons, with myelinated axons, each consisting of about 50 lamellae, and 4-6 μ m in diameter. This histologic structure forms the basis of uniform conduction velocity, which is an important functional feature. Throughout the length of the auditory nerve, there is a trophic arrangement of afferent fibers, with 'basal' fibers wrapped over the centrally placed 'apical' fibers in a twisted rope-like fashion. Spoendlin (Spoendlin, H. H. in Naunton, R. F., Fernadex, C. eds., "Evoked Electrical Activity in the Auditory Nervous System", London, Academic Press, pp. 21-39, (1978)) identified two types of afferent neurons in the spiral ganglion on the basis of morphologic differences: type I cells (95%) are bipolar and have myelinated cell bodies and axons that project to the inner hair cells. Type II cells (5%) are monopolar with unmyelinated axons and project to the outer hair cells of the organ of Corti. Each inner hair cell is innervated by about 20 fibers, each of which synapses on only one cell. In contrast, each outer hair cell is innervated by approximately six fibers, and each fiber branches to supply approximately 10 cells. Within the cochlea, the fibers divide into: 1) an inner spiral group, which arises primarily ipsilaterally and synapses with the afferent neurons to the inner hair cells, and 2) a more numerous outer radial group, which arises mainly contralaterally and synapses directly with outer hair cells. There is a minimal threshold at one frequency, the characteristic or best frequency, but the threshold rises sharply for frequencies above and below this level (Pickles, J.O. in "Introduction to the Physiology of Hearing", London, Academic Press, pp. 71-106, (1982)). Single auditory nerve fibers therefore appear to behave as band-pass filters.

- 14 -

The basilar membrane vibrates preferentially to different frequencies, at different distances along its length, and the frequency selectivity of each cochlear nerve fiber is similar to that of the inner hair cell to which the fiber is connected. Thus, each cochlear nerve fiber exhibits a tuning curve covering a different range of frequencies from its neighboring fiber (Evans, E.F. in Beagley H.A. ed., "Auditory investigation: The Scientific and Technological basis", New York, Oxford University Pressm (1979)). By this mechanism, complex sounds are broken down into component frequencies (frequency resolution) by the filters of the inner ear.

Impairment anywhere along the auditory pathway, from the external auditory canal to the central nervous system, may result in hearing loss. The auditory apparatus can be subdivided into the external and middle ear, inner ear and auditory nerve and central auditory pathways. Auditory information in humans is transduced from a mechanical signal to a neurally conducted electrical impulse by the action of approximately 15,000 epithelial cells (hair cells) and 30,000 first-order neurons (spiral ganglion cells) in the inner ear. All central fibers of spiral ganglion neurons form synapses in the cochlear nucleus of the pontine brainstem. The number of neurons involved in hearing increases dramatically from the cochlea to the auditory brain stem and the auditory cortex. All auditory information is transduced by only 15,000 hair cells, of which the so-called inner hair cells, numbering 3500, are critically important, since they form synapses with approximately 90 percent of the 30,000 primary auditory neurons. Thus, damage to a relatively few cells in the auditory periphery can lead to substantial hearing loss. Hence, most causes of sensorineural loss can be ascribed to lesions in the inner ear (Nadol, J.B., New England Journal of Medicine, (1993), 329:1092-1102).

- 15 -

Hearing loss can be on the level of conductivity, sensorineural and central level. Conductive hearing loss is caused by lesions involving the external or middle ear, resulting in the destruction of the normal pathway of airborne sound amplified by the tympanic membrane and the ossicles to the inner ear fluids. Sensorineural hearing loss is due to lesions of the central auditory pathways. These consist of the cochlear and dorsal olivary nucleus complex, inferior colliculi, medial geniculate bodies, auditory cortex in the temporal lobes and interconnecting afferent and efferent fiber tracts (Adams R.D. and Maurice, V., eds., in "Principles of Neurology", (1989), McGraw-Hill Information Services Company, pp. 226-246).

Trauma due to acoustic overstimulation is another leading cause of deafness. There is individual susceptibility to trauma from noise. Clinically important sensorineural hearing loss may occur in some people exposed to high-intensity noise, even below levels approved by the Occupational Safety and Health Agency (Osguthorpe, J.D., ed., Washington D.C., American Academy of Otolaryngology-Head and Neck Surgery Foundation, (1988)).

Demyelinating processes, such as multiple sclerosis, may cause sensorineural hearing loss (Noffsinger, D., et al., Acto Otolaryngol. Suppl. (Stockh.) (1972), 303:1-63). More recently, a form of immune-mediated sensorineural hearing loss has been recognized (McCabe, B.F., Ann. Otol. Rhinol. Laryngol. (1979), 88:585-9). The hearing loss is usually bilateral, is rapidly progressive (measured in weeks and months), and may or may not be associated with vestibular symptoms.

A variety of tumors, both primary and metastatic, can produce either a conductive hearing loss, or a sensorineural hearing loss, by invading the inner ear or auditory nerve (Houck, J.R., et al., Otolaryngol. Head Neck Surg. (1992), 106:92-7). A variety of degenerative

- 16 -

disorders of unknown cause can produce sensorineural hearing loss. Meniere's syndrome (Nadol, J.B., ed., "Meniere's Disease: Pathogenesis, Pathophysiology, Diagnosis, And Treatment," Amsterdam: Kugler & Ghedini (1989)), characterized by fluctuating sensorineural hearing loss, episodic vertigo, and tinnitus, appears to be caused by a disorder of fluid homeostasis within the inner ear, although the pathogenesis remains unknown. Sudden idiopathic sensorineural hearing loss (Wilson, W.R., et al., Arch. Otolaryngol. (1980), 106:772-6), causing moderate-to-severe sensorineural deafness, may be due to various causes, including inner ear ischemia and viral labyrinthitis.

Regardless of the cause, there exists a need to prevent or treat sensorineural hearing loss. The present invention provides such a method.

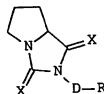
- 17 -

BRIEF SUMMARY OF THE INVENTION

The present invention is directed to novel hydantoin derivative compounds, and their preparation and use for treating neurodegenerative disorders, for treating alopecia and related hair loss disorders, for treating vision disorders and/or improving vision, for treating memory impairment and/or enhancing memory performance, and for treating sensorineural hearing loss.

These compounds stimulate neuronal regeneration and outgrowth and as such are useful for treating neurological disorders and neurodegenerative diseases. These compounds also promote hair growth and as such are useful for treating hair loss disorders. These compounds also are useful for treating vision disorders, improving vision, treating memory impairment, enhancing memory performance, or treating hearing loss. A preferred feature of the compounds of the present invention is that they do not exert any significant immunosuppressive activity and/or are non-immunosuppressive.

A preferred embodiment of this invention is a compound having the formula I:



where

each X independently is O, S, or NR₂;
R₂ is selected from the group consisting of cyano, nitro, hydrogen, C₁-C₄ alkyl, hydroxy, and C₁-C₄ alkoxy;

30

- 18 -

D is a direct bond or a C₁-C₆ alkyl or alkenyl;
R is selected from the group consisting of
hydrogen, phenyl, biphenyl, cyclopropyl,
cyclobutyl, cyclopentyl, cycloheptyl,
5 cyclooctyl, naphthyl, 1,2,3,4-
tetrahydronaphthyl, indenyl, azulenyl,
fluorenyl, anthracenyl, isoindolyl, indoliny,
benzofuranyl, benzothiophenyl, indazolyl,
benzimidazolyl, tetrahydrofuranly,
10 tetrahydropyranly, pyridyl, pyrrolyl,
pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl,
quinolinyl, isoquinolinyl,
tetrahydroquinolinyl, quinolizinyl, furyl,
benzofuranyl, thiophenyl, imidazolyl,
15 oxazolyl, benzoxazolyl, benzoxazinyl,
thiazolyl, isoxazolyl, isotriazolyl,
oxadiazolyl, triazolyl, thiadiazolyl,
pyridazinyl, pyrimidinyl, pyrazinyl,
triazinyl, trithianyl, indolizinyl, pyrazolyl,
20 pyrazolinyl, pyrazolidinyl, benzopyranly,
thienyl, tetrahydroisoquinolinyl, cinnolinyl,
phthalazinyl, quinazolinyl, quinoxalinyl,
naphthyridinyl, pteridinyl, carbazolyl,
phenazinyl, phenothiazinyl, phenoxazinyl, and
25 adamantyl;

wherein R may be optionally substituted with one
substituent which is selected from the group
consisting of hydrogen, halo, hydroxyl, nitro,
trifluoromethyl, C₁-C₆ straight or branched chain
30 alkyl, C₂-C₆ straight or branched chain alkenyl, C₁-
C₆ alkoxy, C₂-C₆ alkenyloxy, phenyl, phenoxy,
benzyloxy, and amino;
or a pharmaceutically acceptable salt, ester, or solvate
thereof;

35 wherein when R is hydrogen, D is a C₃-C₇ alkyl or C₃-

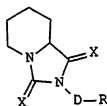
- 19 -

C₆ alkenyl;

wherein when R is phenyl, R must be substituted with phenyl, hydroxyl, trifluoromethyl, C₂-C₆ straight or branched chain alkyl or alkenyl, C₃-C₆ alkoxy or C₂-C₆ alkenyloxy, phenoxy, or benzyloxy;

wherein when R is 4-trifluoromethylphenyl, both X substituents must be O.

Another preferred embodiment of this invention is a compound of formula II:



II

where

each X independently is O, S, or NR₂;

R₂ is selected from the group consisting of cyano, nitro, hydrogen, C₁-C₄ alkyl, hydroxy, and C₁-C₄ alkoxy;

D is a direct bond or a C₁-C₄ alkyl or alkenyl;

R is selected from the group consisting of hydrogen, phenyl, biphenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 1,2,3,4-tetrahydronaphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, indolyl, isoindolyl, indolinyl, benzofuranyl, benzothiophenyl, indazolyl, benzimidazolyl, tetrahydrofuranyl, tetrahydropyranyl, pyridyl, pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinolizinyl, furyl, thiophenyl, imidazolyl, oxazolyl,

- 20 -

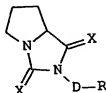
benzopyranyl, thiazolyl, isotriazolyl,
 oxadiazolyl, triazolyl, thiadiazolyl,
 pyridazinyl, pyrimidinyl, pyrazinyl,
 triazinyl, trithianyl, indolizinyl, pyrazolyl,
 5 pyrazolinyl, pyrazolidinyl, thienyl,
 tetrahydroisoquinolinyl, cinnolinyl,
 phthalazinyl, quinazolinyl, naphthyridinyl,
 pteridinyl, carbazolyl, acridinyl, phenazinyl,
 phenothiazinyl, phenoxazinyl, and adamantyl;
 10 wherein R may be optionally substituted with one
 substituent which is selected from the group
 consisting of hydrogen, halo, hydroxyl, nitro,
 trifluoromethyl, C₁-C₆ straight or branched chain
 alkyl, C₂-C₆ straight or branched chain alkenyl, C₁-
 15 C₄ alkoxy, C₂-C₄ alkenyloxy, phenyl, phenoxy,
 benzyloxy, and amino;
 or a pharmaceutically acceptable salt, ester, or solvate
 thereof;

wherein when R is hydrogen, D is a C₃-C₈ alkyl or
 20 alkenyl;

wherein when R is phenyl, R must be substituted
 with C₂-C₃ or C₅-C₆ straight or branched chain alkyl or
 alkenyl, C₃-C₄ alkoxy or C₂-C₄ alkenyloxy, phenyl,
 phenoxy, benzyloxy, or amino.

25 Another preferred embodiment of this invention is a
 pharmaceutical composition containing:

(i) an effective amount of a hydantoin derivative
 compound of formula III:



III

30 where

each X independently is O, S, or NR₂;

R₂ is selected from the group consisting of

- 21 -

cyano, nitro, hydrogen, C₁-C₄ alkyl, hydroxy, and C₁-C₄ alkoxy;

D is a direct bond or C₁-C₈ alkyl or alkenyl;

R is hydrogen, or an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring;

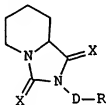
wherein R is optionally substituted with one substituent selected from the group consisting of hydrogen, halo, hydroxyl, nitro, trifluoromethyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, C₁-C₄ alkoxy, C₂-C₄ alkenyloxy, phenyl, phenoxy, benzyloxy, and amino; and

(ii) a pharmaceutically acceptable carrier.

Another preferred embodiment of this invention is a pharmaceutical composition containing:

(i) an effective amount of a hydantoin derivative compound of formula IV:

IV



where

each X independently is O, S, or NR₂;

R₂ is selected from the group consisting of cyano, nitro, hydrogen, C₁-C₄ alkyl, hydroxy, and C₁-C₄ alkoxy;

D is a direct bond or C₁-C₈ alkyl or alkenyl;

R is hydrogen, or an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring;

wherein R is optionally substituted with one substituent selected from the group consisting of hydrogen, halo, hydroxyl, nitro, trifluoromethyl,

- 22 -

C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, C₁-C₄ alkoxy, C₂-C₄ alkenyloxy, phenyl, phenoxy, benzyloxy, and amino; and

5 (ii) a pharmaceutically acceptable carrier.

For neurotrophic compositions, a neurotrophic factor different from the present inventive compounds may also be administered or otherwise included in the composition.

10 Another preferred embodiment of the invention is a method of treating a neurological disorder in an animal, comprising administering to the animal an effective amount of the compound of formulae III or IV to stimulate growth of damaged peripheral nerves or to
15 promote neuronal regeneration.

Another preferred embodiment of the invention is a method of stimulating growth of damaged peripheral nerves, comprising administering to a damaged peripheral nerve an effective amount of the compound of formulae
20 III or IV to stimulate or promote growth of the damaged peripheral nerve.

Another preferred embodiment of the invention is a method of promoting neuronal regeneration and growth in animals, comprising administering to an animal an
25 effective amount of the compound of formulae III or IV to promote neuronal regeneration.

Another preferred embodiment of the invention is a method of preventing neurodegeneration in animals, comprising administering to an animal an effective
30 amount of the compound of formulae III or IV to prevent neurodegeneration.

Another preferred embodiment of the invention is a method for treating alopecia or promoting hair growth in an animal, comprising administering to an animal an
35 effective amount of the compound of formulae III or IV.

- 23 -

Another preferred embodiment of this invention is a method for treating a vision disorder, improving vision, treating memory impairment, enhancing memory performance, or treating sensorineural hearing loss in
5 an animal, comprising administering to an animal an effective amount of the compound of formula III or IV.

The present invention further contemplates a process for preparing the hydantoin derivative compounds of the invention, comprising acidifying an intermediate
10 compound.

The present invention further contemplates the compound(s) of the invention for use in treatment of a disease. In particular, the present invention contemplates the compound(s) of the invention for use in
15 treatment of the disorders enumerated herein.

The invention further contemplates the compound(s) of the invention for use in the preparation of a medicament or pharmaceutical composition. In particular, the invention contemplates the compound(s)
20 of the invention for use in the preparation of a medicament or pharmaceutical composition for treatment of the disorders enumerated herein.

The invention also provides for the use of compound(s) of the invention for treating a disease. In particular, the invention provides for the use of
25 compound(s) of the invention for treating the disorders enumerated herein.

The invention also provides for the use of compound(s) of the invention in the manufacture of a medicament or pharmaceutical composition. In particular, the invention provides for the use of
30 compound(s) of the invention in the manufacture of a medicament or pharmaceutical composition for the treatment of the disorders enumerated herein. Such
35 pharmaceutical compositions include, as appropriate to

- 24 -

- the specific disorder, topical, systemic, oral or injectable formulations. It is further contemplated that the compound(s) of the invention may be administered with an effective amount of a second
- 5 therapeutic agent for the treatment of the enumerated disorders. A variety of pharmaceutical formulations and different delivery techniques are described in further detail below.

- 25 -

DETAILED DESCRIPTION OF THE INVENTIONDefinitions

"Alkenyl" means a branched or unbranched unsaturated hydrocarbon chain comprising a designated number of carbon atoms. For example, C₂-C₆ straight or branched alkenyl hydrocarbon chain contains 2 to 6 carbon atoms having at least one double bond, and includes but is not limited to substituents such as ethenyl, propenyl, iso-propenyl, butenyl, iso-butenyl, tert-butenyl, n-pentenyl, n-hexenyl, and the like. It is also contemplated as within the scope of the present invention that "alkenyl" may also refer to an unsaturated hydrocarbon chain wherein any of the carbon atoms of said alkenyl are optionally replaced with O, NH, S, or SO₂. For example, carbon 2 of 4-pentene can be replaced with O to form (2-propene)oxymethyl.

"Alkoxy" means the group -OR wherein R is alkyl as herein defined. Preferably, R is a branched or unbranched saturated hydrocarbon chain containing 1 to 6 carbon atoms.

"Alkyl" means a branched or unbranched saturated hydrocarbon chain comprising a designated number of carbon atoms. For example, C₁-C₆ straight or branched alkyl hydrocarbon chain contains 1 to 6 carbon atoms, and includes but is not limited to substituents such as methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, tert-butyl, n-pentyl, n-hexyl, and the like. It is also contemplated as within the scope of the present invention that "alkyl" may also refer to a hydrocarbon chain wherein any of the carbon atoms of said alkyl are optionally replaced with O, NH, S, or SO₂. For example, carbon 2 of n-pentyl can be replaced with O to form propyloxymethyl.

"Alopecia" refers to deficient hair growth and

- 26 -

partial or complete loss of hair, including without limitation androgenic alopecia (male pattern baldness), toxic alopecia, alopecia senilis, alopecia areata, alopecia pelada and trichotillomania. Alopecia results when the pilar cycle is disturbed. The most frequent
5 phenomenon is a shortening of the hair growth or anagen phase due to cessation of cell proliferation. This results in an early onset of the catagen phase, and consequently a large number of hairs in the telogen
10 phase during which the follicles are detached from the dermal papillae, and the hairs fall out. Alopecia has a number of etiologies, including genetic factors, aging, local and systemic diseases, febrile conditions, mental stresses, hormonal problems, and secondary effects of
15 drugs.

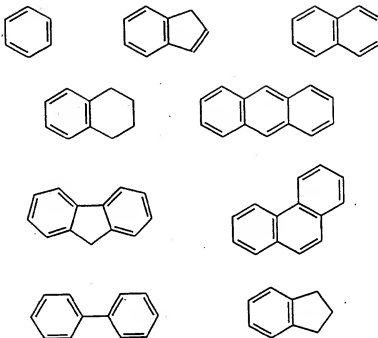
"Aralkyl" refers to alkyl or alkylene (alkenyl) chain which is substituted with aryl, heteroaryl, carbocycle or heterocycle, or alternatively one or more aryl, heteroaryl, carbocycle, or heterocycle(s) which
20 is/are substituted with alkyl or alkenyl, i.e. 'Alkyl/alkylene which is substituted with Ar' or 'Ar which is substituted with alkyl/alkylene'.

"Aryl" or "aromatic" refers to an aromatic carbocyclic or heterocyclic group having a single ring,
25 for example a phenyl ring; multiple rings, for example biphenyl; or multiple condensed rings in which at least one ring is aromatic, for example naphthyl, 1,2,3,4-tetrahydronaphthyl, anthryl, or phenanthryl, which can be unsubstituted or substituted with one or more other
30 substituents as defined above. The substituents attached to a phenyl ring portion of an aryl moiety in the compounds of the invention may be configured in the ortho-, meta-, or para- orientations orientations.

Examples of typical aryl moieties included in the
35 scope of the present invention may include, but are not

- 27 -

limited to, the following:



5 "Carbocycle" or "carbocyclic" refers to an organic cyclic moiety in which the cyclic skeleton is comprised of only carbon atoms, whereas the term "heterocycle" or "heterocyclic" refers to an organic cyclic moiety in which the cyclic skeleton contains one or more heteroatoms selected from nitrogen, oxygen, or sulfur, and which may
10 or may not include carbon atoms. Thus, the term "carbocycle" refers to a carbocyclic moiety containing the indicated number of carbon atoms. The term "C₃-C₈ cycloalkyl", therefore, refers to an organic cyclic substituent in which three to eight carbon atoms form a
15 three, four, five, six, seven, or eight-membered ring, including, for example, a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl ring.

As used herein, "carbocyclic" or "heterocyclic" may also refer to two or more cyclic ring systems, which are
20 fused to form, for example, bicyclic, tricyclic, or other similar bridged ring substituents (e.g. adamantyl) or

- 28 -

multiple condensed ring systems.

"Enhancing memory performance" refers to improving or increasing the mental faculty by which to register, retain or recall past experiences, knowledge, ideas, sensations, thoughts or impressions.

"Eye" refers to the anatomical structure responsible for vision in humans and other animals, and encompasses the following anatomical structures, without limitation: lens, vitreous body, ciliary body, posterior chamber, anterior chamber, pupil, cornea, iris, canal of Schlemm, zonules of Zinn, limbus, conjunctiva, choroid, retina, central vessels of the retina, optic nerve, fovea centralis, macula lutea, and sclera.

"Halo" means at least one fluoro, chloro, bromo, or iodo moiety.

"Heterocycle" or "heterocyclic", as used herein, refers to a saturated, unsaturated or aromatic carbocyclic group having a single ring, multiple fused rings (for example, bicyclic, tricyclic, or other similar bridged ring systems or substituents), or multiple condensed rings, and having at least one hetero atom such as nitrogen, oxygen or sulfur within at least one of the rings. This term also includes "Heteroaryl" which refers to a heterocycle in which at least one ring is aromatic. Any heterocyclic or heteroaryl group can be unsubstituted or optionally substituted with one or more groups, as defined above. Further, bi- or tricyclic heteroaryl moieties may comprise at least one ring which is either completely or partially saturated.

In the context of the invention, useful carbo- and heterocyclic rings include, for example and without limitation, phenyl, benzyl, naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, indolyl, isoindolyl, indolinyl, benzofuranyl, benzothiophenyl, indazolyl, benzimidazolyl, benzthiazolyl, tetrahydrofuranyl, tetrahydropyranyl,

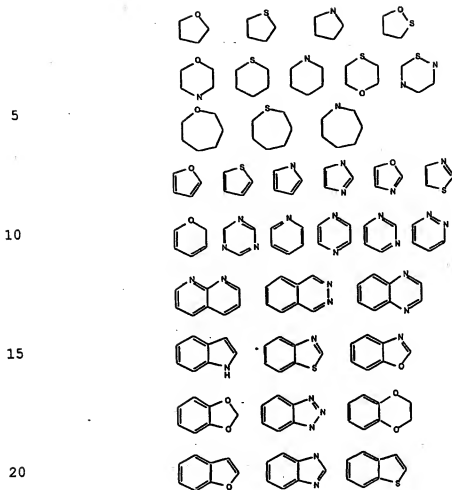
- 29 -

pyridyl, pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinoliziny, furyl, thiophenyl, imidazolyl, oxazolyl, benzoxazolyl, thiazolyl, isoxazolyl, isotriazolyl, 5 oxadiazolyl, triazolyl, thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, trithianyl, indoliziny, pyrazolyl, pyrazolinyl, pyrazolidinyl, thienyl, tetrahydroisoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxaliny, naphthyridinyl, pteridinyl, 10 carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, and adamantyl.

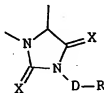
As one skilled in the art will appreciate, such heterocyclic moieties may exist in several isomeric forms, all of which are encompassed by the present invention. For 15 example, a 1,3,5-triazine moiety is isomeric to a 1,2,4-triazine group. Such positional isomers are to be considered within the scope of the present invention. Likewise, the heterocyclic or heteroaryl groups can be bonded to other moieties in the compounds of the present 20 invention. The point(s) of attachment to these other moieties is not to be construed as limiting on the scope of the invention. Thus, by way of example, a pyridyl moiety may be bound to other groups through the 2-, 3-, or 4-position of the pyridyl group. All such configurations 25 are to be construed as within the scope of the present invention.

Examples of heterocyclic or heteroaryl moieties included in the scope of the present invention may include, but are not limited to, the following:

- 30 -



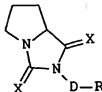
The Condensed Chemical Dictionary (Tenth Edition)
 revised by Gessner G. Hawley (1981) defines "hydantoins"
 25 as compounds having the chemical formula NHCONHCOCH_2 . The
 "hydantoin derivatives" contemplated by the present
 invention have the general structure:



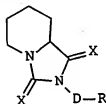
30 wherein the five membered ring depicted is part of a
 bicyclic ring structure and wherein each X independently
 can be O, S, or NR_2 . In particular, one class of hydantoin

- 31 -

derivative compounds contemplated by the present invention has the structure:



- 5 Another class of hydantoin derivative compounds contemplated by the present invention has the structure:



- 10 "Isomers" are different compounds that have the same molecular formula and includes cyclic isomers such as (iso)indole and other isomeric forms of cyclic moieties. "Stereoisomers" are isomers that differ only in the way the atoms are arranged in space. "Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. "Diastereoisomers" are stereoisomers which are not mirror images of each other. "Racemic mixture" means a mixture containing equal parts of individual enantiomers. "Non-racemic mixture" is a mixture containing unequal parts of individual enantiomers or stereoisomers.

- 20 "Memory impairment" refers to a diminished mental registration, retention or recall of past experiences, knowledge, ideas, sensations, thoughts or impressions. Memory impairment may affect short and long-term information retention, facility with spatial relationships, memory (rehearsal) strategies, and verbal retrieval and production. Common causes of memory impairment are age, severe head trauma, brain anoxia or ischemia, alcoholic-nutritional diseases, and drug intoxications. Examples of memory impairment include, without limitation, benign
- 25

- 32 -

forgetfulness, amnesia and any disorder in which memory deficiency is present, such as Korsakoff's amnesic psychosis, dementia and learning disorders.

5 The term "middle-ear" refers to the space between the tympanic membrane and the inner ear. This location is external to all inner ear tissue and an invasive procedure might not be required to access this region if a formulation capable of penetrating through the tympanic membrane is administered. Otherwise, the material will be
10 introduced to the middle ear by injection through the tympanic membrane or, in case repeated administrations are needed, a hole can be made in the tympanic membrane. An opening in the tympanic membrane is a frequent procedure, performed on an office-visit basis, in cases such as
15 infections of the middle ear (usually in children). The opening generally closes spontaneously after a few days.

"Neopsic factors" or "neopsics" refers to compounds useful in treating vision loss, preventing vision degeneration, or promoting vision regeneration.

20 "Neopsis" refers to the process of treating vision loss, preventing vision degeneration, or promoting vision regeneration.

"Neurotrophic" as used herein includes without limitation the ability to stimulate neuronal regeneration
25 or growth, and/or the ability to prevent or treat neurodegeneration.

"Non-immunosuppressive" as used herein refers to the inability of the compounds of the present invention to trigger an immune response when compared to a control such
30 as FK506 or cyclosporin A. Assays for determining immunosuppression are well known to those of ordinary skill in the art. Specific, non-limiting examples of well known assays include PMA and OKT3 wherein mitogens are used to stimulate proliferation of human peripheral blood
35 lymphocytes (PBC) and the compounds are evaluated on their

- 33 -

ability to inhibit such proliferation.

"Ophthalmological" refers to anything about or concerning the eye, without limitation, and is used interchangeably with "ocular," "ophthalmic,"
5 "ophthalmologic," and other such terms, without limitation.

"Pharmaceutically acceptable carrier" as used herein refers to any carrier, diluent, excipient, suspending agent, lubricating agent, adjuvant, vehicle, delivery system, emulsifier, disintegrant, absorbant, preservative,
10 surfactant, colorant, flavorant, or sweetener. For these purposes, the compounds of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir in dosage formulations containing
15 conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, intraperitoneally, intrathecally, intraventricularly, intrasternal and intracranial injection
20 or infusion techniques.

"Pharmaceutically acceptable salt", as used herein, refers to an organic or inorganic salt which is useful in the treatment of a warm-blooded animal in need thereof. Such salts can be acid or basic addition salts, depending
25 on the nature of the inventive compound to be used.

Further, the compounds of the invention may exist as crystalline solids which can be crystallized from common solvents such as ethanol, N,N-dimethyl-formamide, water, or the like. Thus, crystalline forms of the compounds of
30 the invention may exist as solvates and/or hydrates of the parent compounds or their pharmaceutically acceptable salts. All of such forms likewise are to be construed as falling within the scope of the invention.

"Pilar cycle" refers to the life cycle of hair
35 follicles, and includes three phases:

- 34 -

- (1) the anagen phase, the period of active hair growth which, insofar as scalp hair is concerned, lasts about three to five years;
- 5 (2) the catagen phase, the period when growth stops and the follicle atrophies which, insofar as scalp hair is concerned, lasts about one to two weeks; and
- (3) the telogen phase, the rest period when hair progressively separates and finally falls out
10 which, insofar as scalp hair is concerned, lasts about three to four months.

Normally 80 to 90 percent of the follicles are in the anagen phase, less than 1 percent being in the catagen phase, and the rest being in the telogen phase. In the
15 telogen phase, hair is uniform in diameter with a slightly bulbous, non-pigmented root. By contrast, in the anagen phase, hair has a large colored bulb at its root.

"Preventing neurodegeneration" as used herein includes the ability to inhibit or prevent neurodegeneration in
20 patients newly diagnosed as having a neurodegenerative disease, or at risk of developing a new degenerative disease and for inhibiting or preventing further neurodegeneration in patients who are already suffering from or have symptoms of a neurodegenerative disease when
25 the compounds are given concurrently.

"Preventing vision degeneration" as used herein includes the ability to prevent degeneration of vision in patients newly diagnosed as having a degenerative disease affecting vision, or at risk of developing a new
30 degenerative disease affecting vision, and for preventing further degeneration of vision in patients who are already suffering from or have symptoms of a degenerative disease affecting vision.

"Primary ring structure" refers to a 5- or 6-membered
35 ring structure which is depicted in the formula drawings

- 35 -

herein. Such definition shall apply to only one ring structure in any molecule described in this application, regardless of the number or confirmation of any substituent cyclic structures.

5 "Promoting hair growth" refers to maintaining, inducing, stimulating, accelerating, or revitalizing the germination of hair.

"Promoting vision regeneration" refers to maintaining, improving, stimulating or accelerating recovery of, or
10 revitalizing one or more components of the visual system in a manner which improves or enhances vision, either in the presence or absence of any ophthalmologic disorder, disease, or injury.

The term "small molecule" refers to the molecular
15 weight of the compounds of the invention as compared to FK506. Thus, the term "small molecule" includes molecular weights less than about 800 Daltons (m.w.), and novel subranges or limits below the same including about 100 to about 750 m.w., about 150 to about 500 m.w., about 150 to
20 about 350 m.w., about 200 to about 300 m.w., about 210 to about 280 m.w., about 220 to about 260, and about 240 m.w.. The term "spatially small molecule" refers to the capability of the compounds to fit entirely or substantially within the binding cavity of FKBP-12 as
25 compared to FK506.

"Treating" or "treatment" as used herein covers any treatment of a disease and/or condition in an animal, particularly a human, and includes:

(i) preventing a disease and/or condition from
30 occurring in a subject which may be predisposed to the disease and/or condition but has not yet been diagnosed as having it;

(ii) inhibiting the disease and/or condition, i.e., arresting its development; or

35 (iii) relieving the disease and/or condition, i.e.,

- 36 -

causing regression of the disease and/or condition.

"Treating alopecia" refers to:

- (i) preventing alopecia in an animal which may be predisposed to alopecia; and/or
 - 5 (ii) inhibiting, retarding or reducing alopecia; and/or
 - (iii) promoting hair growth; and/or
 - (iv) prolonging the anagen phase of the hair cycle; and/or
 - 10 (v) converting vellus hair to growth as terminal hair.
- Terminal hair is coarse, pigmented, long hair in which the bulb of the hair follicle is seated deep in the dermis. Vellus hair, on the other hand, is fine, thin, non-pigmented short hair in which the hair bulb is located
- 15 superficially in the dermis. As alopecia progresses, the hairs change from the terminal to the vellus type.

"Vision", as used herein, refers to the ability of humans and other animals to process images, and is used interchangeably with "sight", "seeing", and other such

20 terms, without limitation.

"Vision disorder" refers to any disorder that affects or involves vision, including without limitation visual impairment, orbital disorders, disorders of the lacrimal apparatus, disorders of the eyelids, disorders of the

25 conjunctiva, disorders of the cornea, cataracts, disorders of the uveal tract, disorders of the optic nerve or visual pathways, free radical induced eye disorders and diseases, immunologically-mediated eye disorders and diseases, eye injuries, and symptoms and complications of eye disease,

30 eye disorder, or eye injury.

"Visual impairment" refers to any dysfunction in vision including without limitation disturbances or diminution in vision (e.g., binocular, central, peripheral, scotopic), visual acuity for objects near and for, visual

35 field, ocular motility, color perception, adaptation to

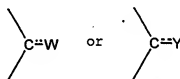
- 37 -

light and dark, accommodation, refraction, and lacrimation.
See *Physicians' Desk Reference (PDR) for Ophthalmology*,
16th Edition, 6:47 (1988).

5 "Warm-blooded animal" includes a mammal, including a
member of the human, equine, porcine, bovine, murine,
canine or feline species. In the case of a human, the term
"warm-blooded animal" may also be referred to as a
"patient". Further, as used herein, "a warm blooded animal
10 in need thereof" refers to a warm-blooded animal which is
susceptible to a disorder due to genetic or environmental
conditions or predispositions. This term also refers to
a warm blooded animal which has already suffered some
degree of injury or damage because of genetic or
15 environmental conditions to which the animal has been
exposed or to which it has been predisposed. Environmental
conditions can include treatment with a therapeutic
compound, as well as other types of injury or insult.

Further, as used throughout the teaching of the
invention, a designation of:

20



25

wherein W or Y is H₂, or similar designations, is meant to
denote that two hydrogen atoms are attached to the noted
carbon and that the bonds to each hydrogen are single
bonds.

- 38 -

Compounds of the Invention

The present invention relates to the surprising discovery that the inventive hydantoin and hydantoin derivative compounds are neurotrophic, are able to treat alopecia, are able to treat vision and memory disorders, and are able to treat sensorineural hearing loss. Accordingly, a novel class of hydantoin derivative compounds is provided. A preferred feature of the compounds of the present invention is that they do not exert any significant immunosuppressive activity.

The neurotrophic compounds of this invention can be periodically administered to a patient undergoing treatment for neurological disorders or for other reasons in which it is desirable to stimulate neuronal regeneration and growth, such as in various peripheral neuropathic and neurological disorders relating to neurodegeneration. The compounds of this invention can also be administered to mammals other than humans for treatment of various mammalian neurological disorders.

The novel compounds of the present invention possess an excellent degree of neurotrophic activity. This activity is useful in the stimulation of damaged neurons, the promotion of neuronal regeneration, the prevention of neurodegeneration, and in the treatment of several neurological disorders known to be associated with neuronal degeneration and peripheral neuropathies. The neurological disorders that may be treated include but are not limited to: trigeminal neuralgia, glossopharyngeal neuralgia, Bell's Palsy, myasthenia gravis, muscular dystrophy, amyotrophic lateral sclerosis, progressive muscular atrophy, progressive bulbar inherited muscular atrophy, herniated, ruptured or prolapsed invertebrate disk syndromes, cervical spondylosis, plexus disorders, thoracic outlet

- 39 -

destruction syndromes, peripheral neuropathic such as those caused by lead, dapsone, ticks, prophylia, or Gullain-Barré syndrome, multiple sclerosis, stroke and ischemia associated with stroke, neural paropathy, other
5 neurodegenerative diseases, motor neuron diseases, sciatic crush, peripheral neuropathy, particularly neuropathy associated with diabetes, spinal cord injuries and facial nerve crush, Huntington's Disease, Alzheimer's disease, and Parkinson's disease.

10 The above discussion relating to the utility and administration of the compounds of the present invention also applies to the pharmaceutical compositions of the present invention.

For these purposes, the compounds of the present
15 invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir in dosage formulations containing conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and
20 vehicles. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, intraperitoneally, intrathecally, intraventricularly, intrasternal and intracranial injection or infusion techniques.

25 For oral administration, the compounds of the present invention may be provided in any suitable dosage form known in the art. For example, the compositions may be incorporated into tablets, powders, granules, beads, chewable lozenges, capsules, liquids, aqueous
30 suspensions or solutions, or similar dosage forms, using conventional equipment and techniques known in the art. Tablet dosage forms are preferred. Tablets may contain carriers such as lactose and corn starch, and/or lubricating agents such as magnesium stearate. Capsules
35 may contain diluents including lactose and dried corn

- 40 -

starch. Aqueous suspensions may contain emulsifying and suspending agents combined with the active ingredient.

When preparing dosage form incorporating the compositions of the invention, the compounds may also be blended with conventional excipients such as binders, including gelatin, pregelatinized starch, and the like; lubricants, such as hydrogenated vegetable oil, stearic acid, and the like; diluents, such as lactose, mannose, and sucrose; disintegrants, such as carboxymethylcellulose and sodium starch glycolate; suspending agents, such as povidone, polyvinyl alcohol, and the like; absorbants, such as silicon dioxide; preservatives, such as methylparaben, propylparaben, and sodium benzoate; surfactants, such as sodium lauryl sulfate, polysorbate 80, and the like; colorants such as F.D. & C. dyes and lakes; flavorants; and sweeteners.

Compositions and methods of the invention also may utilize controlled release technology. Thus, for example, the inventive compounds may be incorporated into a hydrophobic polymer matrix for controlled release over a period of days. Such controlled release films are well known to the art. Particularly preferred are transdermal delivery systems. Other examples of polymers commonly employed for this purpose that may be used in the present invention include nondegradable ethylene-vinyl acetate copolymer and degradable lactic acid-glycolic acid copolymers which may be used externally or internally. Certain hydrogels such as poly(hydroxyethylmethacrylate) or poly(vinylalcohol) also may be useful, but for shorter release cycles than the other polymer release systems, such as those mentioned above.

To be effective therapeutically as central nervous system targets, the compounds of the present invention should readily penetrate the blood-brain barrier when

- 41 -

peripherally administered. Compounds which cannot penetrate the blood-brain barrier can be effectively administered by an intraventricular route or other appropriate delivery system suitable for administration to the brain.

5 The compounds of the present invention may be administered in the form of sterile injectable preparations, for example, as sterile injectable aqueous or oleaginous suspensions. These suspensions may be
10 formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparations may also be sterile injectable solutions or suspensions in non-toxic parenterally-acceptable diluents or
15 solvents, for example, as solutions in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as solvents or
20 suspending mediums. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids such as oleic acid and its glyceride derivatives, including olive oil and castor oil, especially in their polyoxyethylated versions, are
25 useful in the preparation of injectables. These oil solutions or suspensions may also contain long-chain alcohol diluents or dispersants.

 The compounds of this invention may also be administered rectally in the form of suppositories.
30 These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at room temperature, but liquid at rectal temperature and, therefore, will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and
35 polyethylene glycols.

- 42 -

The compounds of this invention may also be administered topically, especially when the conditions addressed for treatment involve areas or organs readily accessible by topical application, including
5 neurological disorders of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas.

For topical application to the eye, or ophthalmic use, the compounds can be formulated as micronized
10 suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively for the ophthalmic uses the compounds may be formulated in an
15 ointment such as petrolatum.

For topical application to the skin, the compounds can be formulated in a suitable ointment containing the compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil,
20 liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the compounds can be formulated in a suitable lotion or cream containing the active compound suspended or dissolved in, for example,
25 a mixture of one or more of the following: mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

Topical application for the lower intestinal tract
30 can be effected in a rectal suppository formulation (see below) or in a suitable enema formulation.

Dosage levels on the order of about 0.1 mg to about 10,000 mg of the active ingredient compound are useful in the treatment of the above conditions, with preferred
35 levels of about 0.1 mg to about 1,000 mg. It is

- 43 -

understood, however, that a specific dose level for any particular patient will vary depending upon a variety of factors, including the activity of the specific compound employed; the age, body weight, general health, sex and diet of the patient; the time of administration; the rate of excretion; drug combination; the severity of the particular disease or disorder being treated; and the form of administration. Typically, *in vitro* dosage-effect results provide useful guidance on the proper doses for patient administration. Studies in animal models are also helpful. The considerations for determining the proper dose levels are well known in the art.

The specific dose may be calculated according to considerations of body weight, body surface area or organ size. Further refinement of the calculations necessary to determine the appropriate dosage for treatment involving each of the above mentioned formulations is routinely made by those of ordinary skill in the art and is within the ambit of tasks routinely performed, especially in light of the dosage information and assays disclosed herein. Appropriate dosages may be determined using established assays in conjunction with appropriate dose-response data. One skilled in the art will appreciate that the dosage used in localized formulations of the invention normally will be smaller as compared to that used in a systemic injection or oral administration.

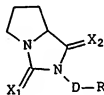
To effectively treat alopecia or promote hair growth, the compounds used in the inventive methods and pharmaceutical compositions must readily affect the targeted areas. For these purposes, the compounds are preferably administered topically to the skin.

The compounds can be administered with other hair revitalizing agents. Specific dose levels for the other

- 44 -

hair revitalizing agents will depend upon the factors previously stated and the effectiveness of the drug combination. Other routes of administration known in the pharmaceutical art are also contemplated by this invention.

Specific embodiments of the inventive compounds are presented in Tables I and II. The present invention contemplates employing the compounds of Tables I and II, below, for use in compositions and methods to prevent and/or treat a neurological disorder in an animal, for use in compositions and methods to treat alopecia and promote hair growth in an animal, for use in compositions and methods to treat a vision disorder, improve vision, treat memory impairment, and enhance memory performance, and for use in compositions and methods to treat a sensorineural hearing loss in an animal, and all the other uses suggested in this specification.



(I)

TABLE I

No.	X_1	X_2	D	R
1	O	O	bond	Naphthyl
2	O	O	bond	2-(Phenyl)phenyl
3	O	O	bond	4-Trifluoromethylphenyl
4	S	O	methyl	Phenyl
5	O	O	hexyl	Hydrogen
6	O	O	bond	2-(Ethyl)phenyl
7	S	O	propyl	Phenyl
8	S	O	ethyl	Phenyl
9	O	O	heptyl	Hydrogen
10	O	O	octyl	Hydrogen
11	S	O	pentyl	3-Pyridyl
12	O	O	propyl	Phenyl

- 45 -

No.	X ₁	X ₂	D	R
13	O	O	bond	3-(Hydroxy) phenyl
14	O	O	bond	4-(tert-butyl)phenyl
15	O	O	bond	2-(Prop-2-enyl)phenyl
16	O	O	bond	3-(Ethoxy)phenyl
17	S	O	bond	Cyclopentyl
18	S	O	bond	Quinoliny
19	O	O	hexyl	Phenyl
20	O	O	ethyl	Phenyl
21	O	O	bond	Cyclopentyl
22	S	S	bond	2-thienyl
23	O	S	bond	2-thienyl
24	O	O	bond	2-oxazolyl
25	S	O	bond	2-furyl
26	O	NH	bond	3-furyl
27	O	NH	hexyl	4-furyl
28	O	S	bond	Adamantyl
29	S	N-CN	bond	Carbazole
30	O	N-NO ₂	bond	Isoquinoline
31	NH	NH	methyl	3-Pyridinyl
32	O	NCH ₃	hexyl	Hydrogen
33	NOH	O	bond	2-Thiazolyl
34	NOCH ₃	S	bond	4-(tert-butyl)phenyl
35	O	S	bond	Cyclohexyl
36	O	O	bond	Phenyl
37	S	O	bond	Phenyl

Preferred compounds of TABLE I are named as follows:

(7aS)-2-(1-Naphthyl)perhydropyrrolo[1,2-c]imidazole-1,3-dione (Compound 1),

30 (7aS)-2-(2'-Phenyl)phenylperhydropyrrolo[1,2-c]imidazole-1,3-dione (Compound 2),

(7aS)-2-(4-(Trifluoromethyl)phenyl)perhydropyrrolo[1,2-c]imidazole-1,3-dione (Compound 3),

2-benzyl-3-thioxo-2,5,6,7,7a-pentahydro-2-azapyrrolizin-1-one (Compound 4),

2-hexyl-2,5,6,7,7a-pentahydro-2-azapyrrolizine-1,3-dione (Compound 5),

2-(2-ethyl)phenyl-2,5,6,7,7a-pentahydro-2-azapyrrolizin-1,3-dione (Compound 6),

- 46 -

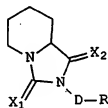
2-(3-phenylpropyl)-3-thioxo-2,5,6,7,7a-pentahydro-2-azapyrrolizin-1-one (Compound 7),

2-(2-phenylethyl)-3-thioxo-2,5,6,7,7a-pentahydro-2-azapyrrolizin-1-one (Compound 8),

5 (7aS)-2-Cyclohexyl-3-thioxoperhydropyrrolo [1,2-c]imidazole-1-one (Compound 35),

2-Phenyl-2,5,6,7,7a-pentahydro-2-azapyrrolizine-1,3-dione (Compound 36), and

10 2-phenyl-3-thioxo-2,5,6,7,7a-pentahydro-2-azapyrrolizin-1-one (Compound 37).



(II)

TABLE II

	No.	X ₁	X ₂	D	R
15	38	O	O	methyl	Phenyl
	39	S	O	methyl	Phenyl
	40	S	O	ethyl	Phenyl
	41	O	O	heptyl	Hydrogen
20	42	O	O	octyl	Hydrogen
	43	S	O	propyl	Phenyl
	44	O	O	hexyl	Hydrogen
	45	O	O	bond	Cyclohexyl
	46	O	O	ethyl	Phenyl
25	47	S	O	heptyl	Hydrogen
	48	O	O	octyl	Hydrogen
	49	S	O	pentyl	3-Pyridyl
	50	O	O	propyl	Phenyl
	51	O	O	bond	3-(Phenoxy)phenyl
30	52	O	O	bond	4-(tert-butyl)phenyl
	53	O	O	bond	2-(Prop-2-enyl)phenyl
	54	O	O	bond	3-(Ethoxy)phenyl
	55	S	O	bond	Cyclopentyl
	56	S	O	bond	Quinoliny

- 47 -

No.	X ₁	X ₂	D	R
57	O	O	hexyl	Phenyl
58	O	O	ethyl	Phenyl
59	O	O	bond	Cyclopentyl
60	S	S	bond	2-thienyl
61	O	S	bond	2-thienyl
62	O	NH	bond	2-oxazolyl
63	S	O	bond	2-furyl
64	O	O	bond	3-furyl
65	S	NH	hexyl	4-furyl
66	O	N-CN	bond	Adamantyl
67	S	N-NO ₂	bond	Carbazole
68	O	S	bond	Adamantyl
69	S	NC ₂ H ₅	bond	2-Pyrazolyl
70	NOH	O	hexyl	Hydrogen
71	NOCH ₃	O	bond	Cyclopentyl
72	O	O	bond	Phenyl
73	S	O	bond	Phenyl
74	O	O	butyl	Hydrogen

20 Preferred compounds of TABLE II are named as follows:

2-Benzyl-2,5,6,7,8,8a-hexahydro-2-azaindolizine-1,3-dione (Compound 38),

25 2-benzyl-3-thioxo-2,5,6,7,8,8a-hexahydro-2-azaindolizin-1-one (Compound 39),

2-(2-phenylethyl)-3-thioxo-2,5,6,7,8,8a-hexahydro-2-azaindolizin-1-one (Compound 40),

2-Heptyl-2,5,6,7,8,8a-hexahydro-2-azaindolizine-1,3-dione (Compound 41),

30 2-Octyl-2,5,6,7,8,8a-hexahydro-2-azaindolizine-1,3-dione (Compound 42),

2-(3-phenylpropyl)-3-thioxo-2,5,6,7,8,8a-hexahydro-2-azaindolizin-1-one (Compound 43),

35 2-hexyl-2,5,6,7,8,8a-hexahydro-2-azaindolizine-1,3-dione (Compound 44),

2-Cyclohexyl-2,5,6,7,8,8a-hexahydro-2-azaindolizine-1,3-dione (Compound 45),

- 48 -

2-phenyl-2,5,6,7,8,8a-hexahydro-2-azaindolizine-1,3-dione (Compound 72),

2-phenyl-3-thioxo-2,5,6,7,8,8a-hexahydro-2-azaindolizine-1-one. (Compound 73), and

5 2-butyl-2,5,6,7,8,8a-hexahydro-2-azaindolizine-1,3-dione (Compound 74).

Other compounds which are hydantoin derivative compounds within the scope of the present invention are those compounds which may possess immunosuppressive, non-
10 immunosuppressive, or other activities as long as they also are useful in treating a disease. In particular, other hydantoin derivative compounds falling within the scope of the present invention are useful for preventing and/or treating neurological disorders, including
15 physically damaged nerves and neurodegenerative diseases; in treating alopecia and promoting hair growth; in treating vision disorders and/or improving vision; in treating memory impairment and/or enhancing memory performance; and/or in treating sensorineural hearing
20 loss.

Pharmaceutical Compositions of the Present Invention

The present invention relates to a pharmaceutical composition comprising:

- 25 (i) an effective amount of a hydantoin derivative compound of formulae III or IV; and
 (ii) a pharmaceutically acceptable carrier.

The present invention also relates to a pharmaceutical composition comprising:

- 30 (i) an effective amount of a hydantoin derivative compound of formulae III or IV for treating neurodegenerative diseases, neurological disorders, and nerve damage, or promoting nerve

- 49 -

growth in animals; and

(ii) a pharmaceutically acceptable carrier.

The present invention also relates to a pharmaceutical composition comprising:

5 (i) an effective amount of a hydantoin derivative compound of formulae III or IV for treating alopecia or promoting hair growth in an animal; and

(ii) a pharmaceutically acceptable carrier.

10 The present invention also relates to a pharmaceutical composition comprising:

(i) an effective amount of a hydantoin derivative compound of formulae III or IV for treating a vision disorder, improving vision, treating
15 memory impairment, or enhancing memory performance in an animal; and

(ii) a pharmaceutically acceptable carrier.

The present invention also relates to a pharmaceutical composition comprising:

20 (i) an effective amount of a hydantoin derivative compound of formulae III or IV for treating sensorineural hearing loss in an animal; and

(ii) a pharmaceutically acceptable carrier.

25 In another preferred embodiment, the novel compounds of the present invention can be administered in pharmaceutical compositions additionally containing other neurotrophic agents such as neurotrophic growth factor, brain derived growth factor, glial derived growth factor, ciliary neurotrophic factor, insulin growth factor and
30 active truncated derivatives thereof, acidic fibroblast growth factor, basic fibroblast growth factor, platelet-

- 50 -

derived growth factors, neurotrophin-3 and neurotrophin 4/5. The dosage level of other neurotrophic drugs will depend upon the factors previously stated and the neurotrophic effectiveness of the drug combination.

5

Methods of the Present Invention

The present invention relates to the use of any of the compounds seen in Tables III and IV, any of the other compounds described above, and other compounds not specifically mentioned or described herein, in the preparation of a medicament for the treatment of a disease. In a preferred embodiment, the disease to be treated includes peripheral neuropathy caused by physical injury or disease state, physical damage to the brain, physical damage to the spinal cord, stroke associated with brain damage, Alzheimer's Disease, Parkinson's Disease, amyotrophic lateral sclerosis, and Huntington's Disease.

The present invention also relates to the use of any of the hydantoin derivative compounds described herein for the treatment of a disease. In particular, the disease to be treated includes the above-mentioned neuropathies, neurological disorders, and neurological damage.

The present invention also relates to a method for treating alopecia or promoting hair growth in an animal, which comprises administering to said animal an effective amount of a hydantoin derivative compound. The present invention also relates to using the inventive compounds and compositions in the preparation of a medicament for the treatment of alopecia or promoting hair growth in an animal.

The inventive method is particularly useful for

- 51 -

5 treating male pattern alopecia, alopecia senilis, alopecia areata, alopecia resulting from skin lesions or tumors, alopecia resulting from cancer therapy such as chemotherapy and radiation, and alopecia resulting from systematic disorders such as nutritional disorders and internal secretion disorders..

10 The present invention also relates to a method for treating a vision disorder, improving vision, treating memory impairment, or enhancing memory performance in an animal, which comprises administering to said animal an effective amount of a hydantoin derivative compound. The present invention also relates to using the inventive compounds and compositions in the preparation of a medicament for the treatment of a vision disorder,
15 improving vision, treating memory impairment, or enhancing memory performance.

The inventive methods are particularly useful for treating various eye disorders including, but not limited to visual disorders, diseases, injuries, and
20 complications, genetic disorders; disorders associated with aging or degenerative vision diseases; vision disorders correlating to physical injury to the eye, head, or other parts of the body resulting from external forces; disorders resulting from environmental factors; disorders resulting from a broad range of diseases; and
25 combinations of any of the above.

In particular, the compositions and methods of the present invention are useful for improving vision, or correcting, treating, or preventing visual (ocular)
30 impairment or dysfunction of the visual system, including permanent and temporary visual impairment, without limitation. The present invention is also useful in preventing and treating ophthalmologic diseases and disorders, treating damaged and injured eyes, and

- 52 -

preventing and treating diseases, disorders, and injuries which result in vision deficiency, vision loss, or reduced capacity to see or process images, and the symptoms and complications resulting from same. The eye diseases and disorders which may be treated or prevented by the compositions and methods of the present invention are not limited with regard to the cause of said diseases or disorders. Accordingly, said compositions and methods are applicable whether the disease or disorder is caused by genetic or environmental factors, as well as any other influences. The compositions and methods of the present invention are particularly useful for eye problems or vision loss or deficiency associated with all of the following, without limitation: aging, cellular or physiological degeneration, central nervous system or neurological disorder, vascular defects, muscular defects, and exposure to adverse environmental conditions or substances.

The compositions and methods of the present invention are particularly useful in correcting, treating, or improving visual impairment, without limitation. Visual impairment in varying degrees occurs in the presence of a deviation from normal in one or more functions of the eye, including (1) visual acuity for objects at distance and near; (2) visual fields; and (3) ocular motility without diplopia. See *Physicians' Desk Reference (PDR) for Ophthalmology, 16th Edition, 6:47 (1988)*. Vision is imperfect without the coordinated function of all three. *Id.*

Said compositions and methods of use are also useful in correcting, treating, or improving other ocular functions including, without limitation, color perception, adaptation to light and dark, accommodation, metamorphopsia, and binocular vision. The compositions

- 53 -

and methods of use are particularly useful in treating, correcting, or preventing ocular disturbances including, without limitation, paresis of accommodation, iridoplegia, entropion, ectropion, epiphora, lagophthalmos, scarring, vitreous opacities, non-reactive pupil, light scattering disturbances of the cornea or other media, and permanent deformities of the orbit.

The compositions and methods of use of the present invention are also highly useful in improving vision and treating vision loss. Vision loss ranging from slight loss to absolute loss may be treated or prevented using said compositions and methods of use. Vision may be improved by the treatment of eye disorders, diseases, and injuries using the compositions and methods of the invention. However, improvements in vision using the compositions and methods of use are not so limited, and may occur in the absence of any such disorder, disease, or injury.

The present invention also relates to a method for treating a sensorineural hearing loss in an animal, which comprises administering to said animal an effective amount of a hydantoin derivative compound. The present invention also relates to using the inventive compounds and compositions in the preparation of a medicament for the treatment of sensorineural hearing loss.

It is further contemplated that administration of an inventive compound will protect hair cells and spiral ganglion neurons from traumatic damage, for example damage caused by noise trauma, acute or chronic treatment with cisplatin and aminoglycoside antibiotics of from damage resulting from a lack of neurotrophic factors resulting from interruption of transport of the factors from the axon to the cell body. Such treatment is expected to allow hair cells and/or auditory neurons to

- 54 -

tolerate intermittent insults from either environmental noise trauma or treatment with ototoxins, and to slow down, prevent or reverse the progressive degeneration of the auditory neurons and hair cells which is responsible for hearing loss in pathological conditions such as presbycusis (age-related hearing loss), inherited sensorineural degeneration, and post-idiopathic hearing losses and to preserve the functional integrity of the inner ear. Such treatment will also support the auditory neurons for better and longer performance of cochlear implants.

It is understood, however, that a specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the severity of the particular disease or disorder being treated and form of administration.

20 K. Test Procedure

The binding to FBKP12 and inhibition of the peptidyl-prolyl isomerase (rotamase) activity of the compounds used in the inventive methods and pharmaceutical compositions can be evaluated by known methods described in the literature (Harding *et al.*, Nature, 1989, 341:758-760; Holt *et al.* J. Am. Chem. Soc., 115:9923-9938). These values are obtained as apparent K_1 's and are presented for representative compounds in TABLE III.

30 The *cis-trans* isomerization of an alanine-proline bond in a model substrate, N-succinyl-Ala-Ala-Pro-Phe-p-nitroanilide, is monitored spectrophotometrically in a chymotrypsin-coupled assay, which releases *para*-

- 55 -

nitroanilide from the *trans* form of the substrate. The inhibition of this reaction caused by the addition of different concentrations of inhibitor is determined, and the data is analyzed as a change in first-order rate constant as a function of inhibitor concentration to yield the apparent K_i values.

In a plastic cuvette are added 950 μ L of ice cold assay buffer (25 mM HEPES, pH 7.8, 100 mM NaCl), 10 μ L of FKBP (2.5 mM in 10 mM Tris-Cl pH 7.5, 100 mM NaCl, 1 mM dithiothreitol), 25 μ L of chymotrypsin (50 mg/mL in 1 mM HCl) and 10 μ L of test compound at various concentrations in dimethyl sulfoxide. The reaction is initiated by the addition of 5 μ L of substrate (succinyl-Ala-Phe-Pro-Phe-para-nitroanilide, 5 mg/mL in 2.35 mM LiCl in trifluoroethanol).

The absorbance at 390 nm versus time is monitored for 90 seconds using a spectrophotometer and the rate constants are determined from the absorbance versus time data files.

TABLE III

In Vitro Test Results

Compound	K_i (nM)
1	>10,000
6	>5,000
35	>10,000

MPTP Model of Parkinson's Disease in Mice

MPTP lesioning of dopaminergic neurons in mice was used as an animal model of Parkinson's Disease. Four week old male CD1 white mice were dosed i.p. with 30 mg/kg of MPTP for 5 days. Inventive compounds (4 mg/kg), or vehicle, were administered s.c. along with the MPTP for 5 days, as well as for an additional 5 days following

- 56 -

cessation of MPTP treatment (Table IV). Inventive compounds (10 mg/kg), or vehicle, were also administered p.o. along with the MPTP for 5 days, as well as for an additional 5 days following cessation of MPTP treatment (Table V). At 18 days following MPTP treatment, the animals were sacrificed and the striata were dissected and homogenized. Immunostaining was performed on sagittal and coronal brain sections using anti-tyrosine hydroxylase Ig to quantitate survival and recovery of dopaminergic neurons. In animals treated with MPTP and vehicle, a substantial loss of functional dopaminergic terminals was observed as compared to non-lesioned animals. In another protocol, test compounds were administered only subsequent to MPTP-induced lesioning. Thus, after animals were treated with MPTP for 5 days, an additional 3 days passed before beginning oral drug treatment on day 8. Animals were treated with inventive compounds (0.4 mg/kg), administered orally, once a day for 5 days total. On day 18, the animals were sacrificed and analyzed as described above. Tables IV and V present the percent recovery of dopaminergic neurons in the first (concurrent dosing) paradigms in animals receiving hydantoin derivative compounds.

Tables IV and V, below, show the remarkable neuroregenerative effects of the inventive hydantoin derivative compounds illustrating the neurotrophic capability of these compounds as a class showing that lesioned animals receiving the hydantoin derivative compounds provide a remarkable recovery of TH-stained dopaminergic neurons.

TABLE IV% Recovery

Compound 1

32.20 %

- 57 -

TABLE V

		<u>% Recovery</u>
	Compound 2	38.40 %
	Compound 3	78.80 %
5	Compound 4	49.30 %
	Compound 7	37.50 %
	Compound 8	42.50 %
	Compound 35	24.40 %
	Compound 38	31.40 %
10	Compound 39	11.20 %
	Compound 40	11.00 %
	Compound 41	8.80 %
	Compound 42	17.40 %
	Compound 43	40.10 %
15	Compound 72	37.20 %
	Compound 74	46.40 %

Percent striatal innervation density was quantitated in brain sections with an anti-tyrosine hydroxylase immunoglobulin, which is indicative of functional dopaminergic neurons. The striatal innervation density of 23% for animals pretreated with only a vehicle and administered a vehicle orally during treatment, is indicative of normal non-lesioned striatal tissue.

25 Striatal innervation density is reduced to 5% for animals pretreated with MPTP and administered a vehicle orally during treatment, and is indicative of MPTP-induced lesioning. Surprisingly, striatal innervation density is increased 8%-13% for animals pretreated with MPTP and

30 administered 0.4 mg/kg orally during treatment, indicating

- 58 -

substantial neuronal regeneration after induction of MPTP-derived lesions.

Synthesis of Compounds of the Invention

5 The compounds for use in the methods and compositions of the invention may be readily prepared by standard techniques of organic chemistry, utilizing the general synthetic pathways depicted below.

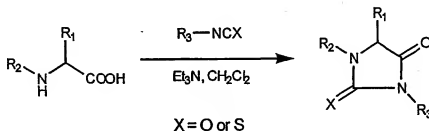
10 In the preparation of the compounds of the invention, one skilled in the art will understand that one may need to protect or block various reactive functionalities on the starting compounds or intermediates while a desired reaction is carried out on other portions of the molecule. After the desired reactions are complete, or at any desired time, normally
15 such protecting groups will be removed by, for example, hydrolytic or hydrogenolytic means. Such protection and deprotection steps are conventional in organic chemistry. One skilled in the art is referred to "Protective Groups in Organic Chemistry," McOmie, ed., Plenum Press, New
20 York, New York; and "Protective Groups in Organic Synthesis," Greene, ed., John Wiley & Sons, New York, N.Y. (1981) for the teaching of protective groups which may be useful in the preparation of compounds of the present invention.

25 The product and intermediates may be isolated or purified using one or more standard purification techniques, including, for example, one or more of simple solvent evaporation, recrystallization, distillation, sublimation, filtration, chromatography, including thin-
30 layer chromatography, HPLC (e.g. reverse phase HPLC), column chromatography, flash chromatography, radial chromatography, trituration, and the like.

The compounds of the present invention may be

- 59 -

prepared by reacting amino acids with isocyanates and isothiocyanates, as shown in the general method of Scheme I:



5

Scheme I

EXAMPLES

The following examples are illustrative of the present invention and are not intended to be limitations thereon. Unless otherwise indicated, all percentages are based upon 100% by weight of the final composition.

EXAMPLE 1

Synthesis of 2-phenyl-2,5,6,7,8,8a-hexahydro-2-azaindolizine-1,3-dione

15

A solution of L-pipecolic acid methyl ester (1.0 g; 3.58 mmol), phenylisocyanate (0.42 ml; 3.93 mmol), and triethylamine (1.64 ml; 11.8 mmol) in methylene chloride (15 ml) was stirred overnight at room temperature. The solvent was removed under vacuum, the residue was dissolved in 50 ml of 50% ethyl acetate in hexane, and the organic phase was washed with water and brine, dried, and concentrated. The residue was purified on a flash column, eluting with 40% ethyl acetate in hexane, to obtain the product as a white solid, ^1H NMR (MeOH, 400 MHz): δ 1.47-1.57 (cm, 3H); 1.62 (bd, 1H, J=9.99); 2.01 (bd, 1H, J=10.36); 2.20 (bd, 1H, J=9.88); 2.96 (t, 1H,

25

- 60 -

J=9.35); 4.06-4.17 (m, 2H); 7.35-7.40 (m, 3H); 7.45-7.48 (m, 2H). Anal. Calcd. for: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.93; H, 6.15; N, 12.21. Mp = 186.1 - 186.7 °C.

5

EXAMPLE 2Synthesis of 2-(2-phenylethyl)-3-thioxo-2,5,6,7,7a-pentahydro-2-azapyrrolizin-1-one

A solution of L-proline methyl ester (1.0 g; 6.03 mmol), phenethylisothiocyanate (1.08 ml; 6.63 mmol), and triethylamine (2 ml; 15.07 mmol) in 15 ml of methylene chloride was stirred overnight at room temperature. The reaction was worked up as described previously, and the product purified to deliver a white solid, ¹H NMR (CDCl₃, 400 MHz): δ 1.56-1.62 (m, 1H); 2.10-2.26 (m, 3H); 2.96-3.01 (m, 2H); 3.52-3.58 (m, 1H); 3.92-3.99 (m, 3H); 4.00-4.12 (m, 1H); 7.19-7.31 (m, 5H). Anal. Calcd. for: C, 64.59; H, 6.19; N, 10.76; S, 12.32. Found: C, 64.69; H, 6.13; N, 10.71; S, 12.44. Mp = 61.2-63.5 °C

15

EXAMPLE 32-(3-phenylpropyl)-3-thioxo-2,5,6,7,7a-pentahydro-2-azapyrrolizin-1-one

This example was prepared according to the method previously described. ¹H NMR (CDCl₃, 400 MHz): δ 1.60-1.63 (m, 1H); 2.00-2.06 (m, 2H); 2.12-2.18 (m, 1H); 2.20-2.26 (m, 2H); 2.66 (t, 2H, J=7.65); 3.51-3.57 (m, 1H); 3.80-3.85 (m, 2H); 3.90-3.97 (m, 1H); 4.07-4.12 (m, 1H); 7.15-7.25 (m, 5H). Anal. Calcd. for: C, 65.66; H, 6.61; N, 10.21; S, 11.69. Found: C, 65.66; H, 6.56; N, 10.14; S, 11.71.

25

30

- 61 -

EXAMPLE 4(7aS)-2-Cyclohexyl-3-thioxoperhydropyrrolo[1,2-climidazole-1-one

This example was prepared according to the method previously described. ¹H NMR (CDCl₃, 400 MHz): δ 1.12-1.41 (m, 3H); 1.59-1.65 (m, 4H); 1.69-1.81 (m, 2H); 2.10-2.21 (m, 2H); 2.25-2.38 (m, 3H); 3.61-3.66 (m, 1H); 3.90-3.98 (m, 1H); 4.02-4.13 (m, 1H); 4.44-4.51 (m, 1H). Anal. Calcd. for C₁₂H₁₈N₂O₂S: C, 60.47; H, 7.61; N, 11.75; S, 13.45. Found: C, 60.52; H, 7.60; N, 11.73; S, 13.27.

EXAMPLE 5(7aS)-2-(2'-Phenyl)phenylperhydropyrrolo[1,2-climidazole-1,3-dione

This example was prepared according to the method previously described. ¹H NMR (CDCl₃, 400 MHz): δ 1.00-1.16 (m, 1H); 1.58-2.25 (m, 3H); 3.12-3.22 (m, 1H); 3.57-3.72 (m, 1H); 3.92-4.04 (m, 1H); 7.20-7.52 (m, 9H). Anal. Calcd. for C₁₈H₁₆N₂O₂-0.05 EtOAc: C, 73.67; H, 5.57; N, 9.44. Found: C, 73.50; H, 5.87; N, 9.74.

EXAMPLE 6(7aS)-2-(4-(Trifluoromethyl)phenyl)perhydropyrrolo[1,2-climidazole-1,3-dione

This example was prepared according to the method previously described. ¹H NMR (CDCl₃, 400 MHz): δ 1.82-1.99 (m, 1H); 2.14-2.22 (m, 2H); 2.34-2.39 (m, 1H); 3.34-3.40 (m, 1H); 3.77-3.84 (m, 1H); 4.24-4.29 (m, 1H); 7.67 (d, 2H, J = 8.35); 7.72 (d, 2H, J = 8.60). Anal. Calcd. for C₁₃H₁₁N₂O₂F: C, 54.93; H, 3.90; N, 9.86. Found: C, 55.45; H, 4.26; N, 9.87.

- 62 -

EXAMPLE 7(7aS)-2-(1-Naphthyl)perhydropyrrolo[1,2-climidazole-1,3-dione

This example was prepared according to the method previously described. ¹H NMR (CDCl₃, 300 MHz): δ 1.94-2.03 (m, 1H); 2.05-2.33 (m, 2H); 2.39-2.51 (m, 1H); 3.38-3.44 (m, 1H); 3.83-4.09 (m, 1H); 4.41 (dt, 1H, J = 7.45); 7.38-7.96 (m, 2H). Anal. Calcd. for C₁₆H₁₄N₂O₂: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.05; H, 5.32; N, 10.51.

EXAMPLE 82-Phenyl-2,5,6,7,7a-pentahydro-2-azapyrrolizine-1,3-dione

This example was prepared according to the method previously described. ¹H NMR (CDCl₃, 400 MHz): δ 1.78 (m, 1H); 2.10 (m, 2H); 2.26 (m, 1H); 3.28 (m, 1H); 3.73 (q, 1H); 4.17 (t, 2H); 7.31 (m, 3H); 7.38 (m, 2H).

EXAMPLE 92-benzyl-2,5,6,7,8,8a-hexahydro-2-azaindolizine-1,3-dione

This example was prepared according to the method previously described. ¹H NMR (MeOH, 400 MHz): δ 1.26-1.39 (m, 2H); 1.50-1.57 (m, 1H); 1.7 (bd, 1H, J=10.03); 1.95 (bd, 1H, J=13.56); 2.13 (bd, 1H, J=9.57); 2.89 (td, 1H, J=9.44, 3.52); 3.93 (dd, 1H, J=12.07, 4.26); 4.04-4.09 (m, 1H); 4.61 (s, 2H); 7.24-7.31 (m, 5H). Anal. Calcd. for: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.90; H, 6.61; N, 11.48.

EXAMPLE 102-benzyl-3-thioxo-2,5,6,7,7a-pentahydro-2-azapyrrolizine-1-one

This example was prepared according to the method previously described. ¹H NMR (MeOH, 400 MHz): δ 1.60-1.66

- 63 -

(m, 1H); 2.20-2.26 (m, 3H); 3.50-3.56 (m, 1H); 3.86-3.93 (m, 1H); 4.33-4.37 (m, 1H); 4.95 (d, 2H, J=14.81); 7.20-7.29 (m, 3H); 7.30-7.37 (m, 2H). Anal. Calcd. for: C, 63.39; H, 5.73; N, 11.37; S, 13.02. Found: C, 63.60; H, 5.90; N, 11.21; S, 12.92.

EXAMPLE 112-benzyl-3-thioxo-2,5,6,7,8,8a-hexahydro-2-azaindolizine-1-one

This example was prepared according to the method previously described. ¹H NMR (MeOH, 400 MHz): δ 1.30-1.33 (m, 1H); 1.42-1.45 (m, 1H); 1.69 (q, 1H, J=9.55); 1.82 (bd, 1H, J=13.38); 1.95 (bd, 1H, J=13.55); 2.16 (bd, 1H, J=12.91); 3.09 (td, 1H, J=3.27, 13.11); 4.07 (dd, 1H, J=7.18, 4.13); 4.76 (dd, 1H, J=9.46, 3.46); 4.97 (d, 2H); 7.22-7.29 (m, 3H); 7.36-7.38 (m, 2H). Anal. Calcd. for: C, 64.59; H, 6.19; N, 10.76; S, 12.32. Found: C, 64.69; H, 6.22; N, 10.83; S, 12.32.

EXAMPLE 122-(2-phenylethyl)-3-thioxo-2,5,6,7,8,8a-hexahydro-2-azaindolizine-1-one

This example was prepared according to the method previously described. ¹H NMR (CDCl₃, 400 MHz): δ 1.22-1.26 (m, 1H); 1.44-1.49 (m, 2H); 1.82 (bd, 1H, J=10.00); 1.95 (bd, 1H, J=11.04); 2.18 (bd, 1H, J=10.11); 2.95-3.03 (m, 3H); 3.76 (dd, 1H, J=4.34, 12.14); 4.01-4.06 (m, 2H); 4.83 (bd, 1H, J=13.32); 7.19-7.29 (m, 5H). Anal. Calcd. - with 0.20 H₂O for: C, 64.81; H, 6.67; N, 10.08; S, 11.53. Found: C, 64.64; H, 6.60; N, 9.92; S, 11.57.

EXAMPLE 132-heptyl-2,5,6,7,8,8a-hexahydro-2-azaindolizine-1,3-dione

This example was prepared according to the method

- 64 -

previously described. ¹H NMR (MeOH, 400 MHz): δ 0.87-0.91 (m, 4H); 1.30 (bs, 9H); 1.53-1.59 (m, 3H); 1.73 (bd, 1H, J=13.17); 1.94 (bd, 1H, J=10.43); 2.13 (bd, 1H, J=12.69); 2.88 (td, 1H, J=3.50, 9.57); 3.30 (s, 1H); 3.43-3.47 (m, 1H); 3.89 (dd, 1H, J=4.20, 11.94); 4.06 (dd, 1H, J=3.85, 12.85). Anal. Calcd. for: C, 66.63; H, 9.59; N, 11.10. Found: C, 66.37; H, 9.56; N, 10.99.

EXAMPLE 14

2-octyl-2,5,6,7,8,8a-hexahydro-2-azaindolizine-1,3-dione

This example was prepared according to the method previously described. ¹H NMR (CDCl₃, 400 MHz): δ 0.87 (bs, 3H); 1.28 (bs, 11H); 1.36-1.50 (m, 2H); 1.59 (bs, 2H); 1.97 (bd, 1H, J=11.28); 2.18 (bd, 1H, J=13.16); 2.22 (bd, 1H, J=13.12); 2.81 (td, 1H, J=3.45, 12.86); 3.47 (t, 2H, J=7.39); 3.72 (dd, 1H, J=4.24, 11.96); 4.17 (dd, 1H, J=4.71, 13.31). Anal. Calcd. for: C, 67.63; H, 9.84; N, 10.52. Found: C, 67.89; H, 10.01; N, 10.42.

EXAMPLE 15

2-phenyl-3-thioxo-2,5,6,7,8,8a-hexahydro-2-azaindolizine-1-one

This example was prepared according to the method previously described. ¹H NMR (MeOH, 400 MHz): δ 1.54-1.66 (m, 3H); 1.88 (bd, 1H, J=8.49); 1.90-2.08 (m, 1H); 2.35 (bd, 1H, J=11.96); 3.10 (td, 1H, J=3.68, 12.85); 4.04 (dd, 1H, J=4.48, 11.67); 4.93 (dd, 1H, J=1.95, 11.03); 7.30-7.32 (m, 2H); 7.41-7.51 (m, 3H). Anal. Calcd. for: C, 63.39; H, 5.73; N, 11.37; S, 13.02. Found: C, 63.53; H, 5.82; N, 11.32; S, 13.07.

- 65 -

EXAMPLE 162-(3-phenylpropyl)-3-thioxo-2,5,6,7,8,8a-hexahydro-2-azaindolizine-1-one

This example was prepared according to the method
5 previously described. ¹H NMR (CDCl₃, 400 MHz): δ 1.23-
1.29 (m, 2H); 1.47-1.54 (m, 2H); 1.79 (bd, 1H, J=10.18);
1.82-2.08 (m, 2H); 2.22 (bd, 1H, J=13.02); 2.67 (t, 2H,
J=7.61); 2.95 (td, 1H, J=3.33, 9.59); 3.71 (dd, 1H,
J=4.31, 12.14); 3.85-3.89 (m, 2H); 4.82 (dd, 1H, J=4.45,
10 13.18); 7.14-7.28 (m, 5H). Anal. Calcd. for: C, 66.63; H,
6.99; N, 9.71; S, 11.12. Found: C, 66.75; H, 7.08; N,
9.67; S, 11.21.

EXAMPLE 172-butyl-2,5,6,7,8,8a-hexahydro-2-azaindolizine-1,3-dione

This example was prepared according to the method
15 previously described. ¹H NMR (CDCl₃, 400 MHz): δ 0.92
(t, 3H, J=7.33); 1.24-1.63 (cm, 7H); 1.73 (bd, 1H,
J=8.55); 1.98 (bd, 1H, J=13.44); 2.21 (bd, 1H, J=9.90);
2.81 (td, 1H, J=3.56, 12.78); 3.49 (t, 2H, J=7.34); 3.72
20 (dd, 1H, J=4.26, 11.97); 4.15 (dd, 1H, J=4.74, 13.33).
Anal. Calcd. for: C, 62.83; H, 8.63; N, 13.32. Found: C,
62.57; H, 8.54; N, 13.17.

EXAMPLE 182-hexyl-2,5,6,7,8,8a-hexahydro-2-azaindolizine-1,3-dione

This example was prepared according to the method
25 previously described. ¹H NMR (MeOH, 400 MHz): δ 0.88-
0.91 (m, 3H); 1.25-1.34 (bs, 8H); 1.50-1.58 (m, 3H);
1.71-1.75 (m, 1H); 1.92-1.96 (m, 1H); 2.11-2.15 (m, 1H);
2.85-2.93 (m, 1H); 3.43-3.47 (m, 2H); 3.87-3.91 (m, 1H);
30 4.04-4.08 (m, 1H). Anal. Calcd. with 0.1 EtOAc for: C,
65.12; H, 9.30; N, 11.34. Found: C, 64.87; H, 9.26; N,

- 66 -

11.54.

EXAMPLE 192-hexyl-2,5,6,7,7a-pentahydro-2-azapyrrolizine-1,3-dione

This example was prepared according to the method previously described. ¹H NMR (CDCl₃, 400 MHz): δ 0.85-0.89 (bs, 3H); 1.28 (bs, 7H); 1.59 (m, 1H); 1.63-1.73 (m, 1H); 2.22-2.24 (m, 2H); 2.25-2.27 (m, 1H); 3.21-3.27 (m, 1H); 3.43-3.47 (m, 2H); 3.65-3.72 (m, 1H); 4.06 (dd, 1H, J=1.20, 7.22). Anal. Calcd. for: C, 64.26; H, 8.99; N, 12.49. Found: C, 64.02; H, 9.00; N, 12.42.

EXAMPLE 202-phenyl-3-thioxo-2,5,6,7,7a-pentahydro-2-azapyrrolizine-1-one

This example was prepared according to the method previously described. ¹H NMR (CDCl₃, 400 MHz): δ 1.85-1.93 (m, 1H); 2.21-2.27 (m, 1H); 2.31-2.43 (m, 2H); 3.63-3.69 (m, 1H); 4.04-4.11 (m, 1H); 4.38 (dd, 1H, J=6.96, 10.39); 7.25-7.32 (m, 2H); 7.40-7.51 (m, 3H). Mp = 187.3-189.7 °C. Anal. Calcd. for: C, 62.04; H, 5.21; N, 12.06; S, 13.80. Found: C, 61.85; H, 5.26; N, 12.01; S, 13.97.

EXAMPLE 21

A lotion comprising the following composition may be prepared.

25		(%)
	95% Ethanol	80.0
	a hydantoin derivative	10.0
	α-Tocopherol acetate	0.01
30	Ethylene oxide (40 mole) adducts of hardened castor oil	0.5

- 67 -

purified water	9.0
perfume and dye	q.s.

5 Into 95% ethanol are added a hydantoin derivative, α -tocopherol acetate, ethylene oxide (40 mole) adducts of hardened castor oil, perfume, and a dye. The resulting mixture is stirred and dissolved, and purified water is added to the mixture to obtain a transparent liquid lotion.

10 5 ml of the lotion may be applied once or twice per day to a site having marked baldness or alopecia.

EXAMPLE 22

A lotion comprising the following composition shown may be prepared.

		(%)
15	95% Ethanol	80.0
	a hydantoin derivative	0.005
	Hinokitol	0.01
	Ethylene oxide (40 mole) adducts of hardened castor oil	0.5
20	Purified water	19.0
	Perfume and dye	q.s.

25 Into 95% ethanol are added a hydantoin derivative, hinokitol, ethylene oxide (40 mole) adducts of hardened castor oil, perfume, and a dye. The resulting mixture is stirred, and purified water is added to the mixture to obtain a transparent liquid lotion.

The lotion may be applied by spraying once to 4 times per day to a site having marked baldness or alopecia.

30

EXAMPLE 23

An emulsion may be prepared from A phase and B phase

- 68 -

having the following compositions.

	(A phase)	(%)
	Whale wax	0.5
	Cetanol	2.0
5	Petrolatum	5.0
	Squalane	10.0
	Polyoxyethylene (10 mole) monostearate	2.0
	Sorbitan monooleate	1.0
	a hydantoin derivative	0.01
10	(B phase)	(%)
	Glycerine	10.0
	Purified water	69.0
	Perfume, dye, and preservative	q.s.

15 The A phase and the B phase are respectively heated and melted and maintained at 80°C. Both phases are then mixed and cooled under stirring to normal temperature to obtain an emulsion.

20 The emulsion may be applied by spraying once to four times per day to a site having marked baldness or alopecia.

EXAMPLE 24

A cream may be prepared from A phase and B phase having the following compositions.

	(A Phase)	(%)
25	Fluid paraffin	5.0
	Cetostearyl alcohol	5.5
	Petrolatum	5.5
	Glycerine monostearate	33.0
30	Polyoxyethylene (20 mole) 2-octyldodecyl ether	3.0

- 69 -

5	Propylparaben	0.3
	(B Phase)	(%)
	a hydantoin derivative	0.8
	Glycerine	7.0
	Dipropylene glycol	20.0
	Polyethylene glycol 4000	5.0
	Sodium Hexametaphosphate	0.005
	Purified water	44.895

10 The A phase is heated and melted, and maintained at 70°C. The B phase is added into the A phase and the mixture is stirred to obtain an emulsion. The emulsion is then cooled to obtain a cream.

15 The cream may be applied once to 4 times per day to a site having marked baldness or alopecia.

EXAMPLE 25

A topical liquid comprising the following composition may be prepared.

20		(%)
	Polyoxyethylene butyl ether	20.0
	Ethanol	50.0
	a hydantoin derivative	0.001
	Propylene glycol	5.0
	Polyoxyethylene hardened castor oil	0.4
	derivative (ethylene oxide 80 mole adducts)	
	Perfume	q.s.
25	Purified water	q.s.

30 Into ethanol are added polyoxypropylene butyl ether, propylene glycol, polyoxyethylene hardened castor oil, a hydantoin derivative, and perfume. The resulting mixture

- 70 -

is stirred, and purified water is added to the mixture to obtain a liquid.

The liquid may be applied once to 4 times per day to a site having marked baldness or alopecia.

5

EXAMPLE 26

A shampoo comprising the following composition may be prepared.

		(%)
	Sodium laurylsulfate	5.0
10	Triethanolamine laurylsulfate	5.0
	Betaine lauryldimethylaminoacetate	5.0
	Ethylene glycol distearate	2.0
	Polyethylene glycol	5.0
	a hydantoin derivative	5.0
15	Ethanol	2.0
	Perfume	0.3
	Purified water	69.7

20 Into 69.7 of purified water are added 5.0 g of sodium laurylsulfate, 5.0 g of triethanolamine laurylsulfate, 6.0 g of betaine lauryldimethyl-aminoacetate. Then a mixture obtained by adding 5.0 g of a hydantoin derivative, 5.0 g of polyethylene glycol, and 2.0 g of ethylene glycol distearate to 2.0 g of ethanol, followed by stirring, and
25 0.3 g of perfume are successively added. The resulting mixture is heated and subsequently cooled to obtain a shampoo.

The shampoo may be used on the scalp once or twice per day.

30

EXAMPLE 27

A patient is suffering from alopecia senilis. A

- 71 -

hydantoin derivative compound, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

5

EXAMPLE 28

A patient is suffering from male pattern alopecia. A hydantoin derivative compound, or a pharmaceutical composition comprising the same, or a pharmaceutical composition comprising the same may be administered to the patient. Increased hair growth is expected to occur following treatment.

10

EXAMPLE 29

A patient is suffering from alopecia areata. A hydantoin derivative compound, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

15

EXAMPLE 30

A patient is suffering from hair loss caused by skin lesions. A hydantoin derivative compound, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

20

EXAMPLE 31

A patient is suffering from hair loss caused by tumors. A hydantoin derivative compound, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

25

EXAMPLE 32

30

A patient is suffering from hair loss caused by a

- 72 -

systematic disorder, such as a nutritional disorder or an internal secretion disorder. A hydantoin derivative compound, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

EXAMPLE 33

A patient is suffering from hair loss caused by chemotherapy. A hydantoin derivative compound, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

EXAMPLE 34

A patient is suffering from hair loss caused by radiation. A hydantoin derivative compound, or a pharmaceutical composition comprising the same may, be administered to the patient. Increased hair growth is expected to occur following treatment.

EXAMPLE 35

A patient is suffering from a neurodegenerative disease. A hydantoin derivative compound or a pharmaceutical composition comprising the same is administered. It would be expected that the patient would improve their condition or recover.

EXAMPLE 36

A patient is suffering from a neurological disorder. A hydantoin derivative compound or pharmaceutical compositions comprising same is administered. It would be expected that the patient would improve their condition or recover.

EXAMPLE 37

A patient is suffering from stroke. A hydantoin

- 73 -

derivative compound or pharmaceutical compositions comprising same is administered. It would be expected that the patient would improve their condition or recover.

EXAMPLE 38

5 A patient is suffering from Parkinson's Disease. A hydantoin derivative compound or pharmaceutical compositions comprising same is administered. It would be expected that the patient would improve their condition or recover.

10

EXAMPLE 39

 A patient is suffering from Alzheimer's Disease. A hydantoin derivative compound or pharmaceutical compositions comprising same is administered. It would be expected that the patient would improve their condition or recover.

15

EXAMPLE 40

 A patient is suffering from Huntington's Disease. A hydantoin derivative compound or pharmaceutical compositions comprising same is administered. It would be expected that the patient would improve their condition or recover.

20

EXAMPLE 41

 A patient is suffering from a peripheral neuropathy. A hydantoin derivative compound or pharmaceutical compositions comprising same is administered. It would be expected that the patient would improve their condition or recover.

25

EXAMPLE 42

30 A patient is suffering from amyotrophic lateral sclerosis. A hydantoin derivative compound or pharmaceutical compositions comprising same is

- 74 -

administered. It would be expected that the patient would improve their condition or recover.

EXAMPLE 43

5 A patient is suffering from a spinal injury. A hydantoin derivative compound or pharmaceutical compositions comprising same is administered. It would be expected that the patient would improve their condition or recover.

EXAMPLE 44

10 A patient is at risk of suffering from a neurodegenerative disease or neurological disorder. A hydantoin derivative compound or a pharmaceutical composition comprising the same is prophylactically administered. It would be expected that the patient would
15 be prevented from some or all of the effects of the disease or disorder, or would significantly improve their condition or recover over patients who were not pre-treated.

EXAMPLE 45

20 A patient is suffering from macular degeneration. A hydantoin derivative compound as identified above, alone or in combination with one or more other neoplastic factors, or a pharmaceutical composition comprising the same, may be administered to the patient. A reduction in vision loss, prevention of vision degeneration, and/or promotion of
25 vision regeneration are/is expected to occur following treatment.

EXAMPLE 46

30 A patient is suffering from glaucoma, resulting in cupping of the optic nerve disc and damage to nerve fibers. A hydantoin derivative compound as identified above, alone or in combination with one or more other neoplastic factors, or a pharmaceutical composition comprising the same, may be

- 75 -

administered to the patient. A reduction in vision loss, prevention of vision degeneration, and/or promotion of vision regeneration are/is expected to occur following treatment.

5

EXAMPLE 47

A patient is suffering from cataracts requiring surgery. Following surgery, a hydantoin derivative compound as identified above, alone or in combination with one or more other neoplastic factors, or a pharmaceutical composition comprising the same, may be administered to the patient. A reduction in vision loss, prevention of vision degeneration, and/or promotion of vision regeneration are/is expected to occur following treatment.

10

EXAMPLE 48

A patient is suffering from an impairment or blockage of retinal blood supply relating to diabetic retinopathy, ischemic optic neuropathy, or retinal artery or vein blockage. A hydantoin derivative compound as identified above, alone or in combination with one or more other neoplastic factors, or a pharmaceutical composition comprising the same, may be administered to the patient. A reduction in vision loss, prevention of vision degeneration, and/or promotion of vision regeneration are/is expected to occur following treatment.

15

20

25

EXAMPLE 49

A patient is suffering from a detached retina. A hydantoin derivative compound as identified above, alone or in combination with one or more other neoplastic factors, or a pharmaceutical composition comprising the same, may be administered to the patient. A reduction in vision loss, prevention of vision degeneration, and/or promotion of vision regeneration are/is expected to occur following treatment.

30

- 76 -

EXAMPLE 50

A patient is suffering from tissue damage caused by inflammation associated with uveitis or conjunctivitis. A hydantoin derivative compound as identified above, alone or in combination with one or more other neoplastic factors, or a pharmaceutical composition comprising the same, may be administered to the patient. A reduction in vision loss, prevention of vision degeneration, and/or promotion of vision regeneration are/is expected to occur following treatment.

EXAMPLE 51

A patient is suffering from photoreceptor damage caused by chronic or acute exposure to ultraviolet light. A hydantoin derivative compound as identified above, alone or in combination with one or more other neoplastic factors, or a pharmaceutical composition comprising the same, may be administered to the patient. A reduction in vision loss, prevention of vision degeneration, and/or promotion of vision regeneration are/is expected to occur following treatment.

EXAMPLE 52

A patient is suffering from optic neuritis. A hydantoin derivative compound as identified above, alone or in combination with one or more other neoplastic factors, or a pharmaceutical composition comprising the same, may be administered to the patient. A reduction in vision loss, prevention of vision degeneration, and/or promotion of vision regeneration are/is expected to occur following treatment.

EXAMPLE 53

A patient is suffering from tissue damage associated with a "dry eye" disorder. A hydantoin derivative compound

- 77 -

as identified above, alone or in combination with one or more other neoplastic factors, or a pharmaceutical composition comprising the same, may be administered to the patient. A reduction in vision loss, prevention of vision degeneration, and/or promotion of vision regeneration are/is expected to occur following treatment.

EXAMPLE 54

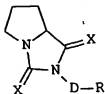
A patient is suffering from sensorineural hearing loss. A hydantoin derivative compound as identified above, alone or in combination with one or more other factors, or a pharmaceutical composition comprising the same, may be administered to the patient. A reduction in hearing loss is expected to occur following treatment.

The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention and all such modifications are intended to be included within the scope of the following claims.

- 78 -

We claim:

1. A compound of the formula:



5 where

each X independently is O, S, or NR₂;

R₂ is selected from the group consisting of
cyano, nitro, hydrogen, C₁-C₄ alkyl, hydroxy,
and C₁-C₄ alkoxy;

10 D is a direct bond or a C₁-C₄ alkyl or alkenyl;

R is selected from the group consisting of
hydrogen, phenyl, biphenyl, cyclopropyl,
cyclobutyl, cyclopentyl, cycloheptyl,
cyclooctyl, naphthyl, 1,2,3,4-
15 tetrahydronaphthyl, indenyl, azulenyl,
fluorenyl, anthracenyl, isoindolyl, indolyl,
benzofuranyl, benzothiophenyl, indazolyl,
benzimidazolyl, tetrahydrofuranyl,
tetrahydropyranyl, pyridyl, pyrrolyl,
20 pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl,
quinolinyl, isoquinolinyl,

tetrahydroquinolinyl, quinoliziny, furyl,
benzofuranyl, thiophenyl, imidazolyl,
oxazolyl, benzoxazolyl, benzoxazinyl,
25 thiazolyl, isoxazolyl, isotriazolyl,
oxadiazolyl, triazolyl, thiadiazolyl,
pyridazinyl, pyrimidinyl, pyrazinyl,
triazinyl, trithianyl, indoliziny, pyrazolyl,
pyrazolinyl, pyrazolidinyl, benzopyranyl,
30 thienyl, tetrahydroisoquinolinyl, cinnolinyl,
phthalazinyl, quinazolinyl, quinoxalinyl,
naphthyridinyl, pteridinyl, carbazolyl,

- 79 -

phenaziny, phenothiaziny, phenoxaziny, and adamantyl;

5 wherein R may be optionally substituted with one substituent which is selected from the group consisting of hydrogen, halo, hydroxyl, nitro, trifluoromethyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, C₁-C₆ alkoxy, C₂-C₆ alkenyloxy, phenyl, phenoxy, benzyloxy, and amino;

10 or a pharmaceutically acceptable salt, ester, or solvate thereof;

wherein when R is hydrogen, D is a C₁-C₆ alkyl or C₂-C₆ alkenyl;

15 wherein when R is phenyl and D is a bond, R must be substituted with phenyl, hydroxyl, trifluoromethyl, C₂-C₆ straight or branched chain alkyl or alkenyl, C₃-C₆ alkoxy or C₂-C₆ alkenyloxy, phenoxy, or benzyloxy;

wherein when R is 4-trifluoromethylphenyl, both X substituents must be O.

20 2. The compound according to claim 1 that is selected from the group consisting of:

(7aS)-2-(1-Naphthyl)perhydropyrrolo[1,2-c]imidazole-1,3-dione,

25 (7aS)-2-(2'-Phenyl)phenylperhydropyrrolo[1,2-c]imidazole-1,3-dione,

(7aS)-2-(4-(Trifluoromethyl)phenyl)perhydropyrrolo[1,2-c]imidazole-1,3-dione,

2-benzyl-3-thioxo-2,5,6,7,7a-pentahydro-2-azapyrrolizin-1-one,

30 2-hexyl-2,5,6,7,7a-pentahydro-2-azapyrrolizin-1,3-dione,

2-(2-ethyl)phenyl-2,5,6,7,7a-pentahydro-2-azapyrrolizin-1,3-dione,

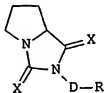
2-(3-phenylpropyl)-3-thioxo-2,5,6,7,7a-pentahydro-

- 80 -

2-azapyrrolizin-1-one, and

2-(2-phenylethyl)-3-thioxo-2,5,6,7,7a-pentahydro-2-azapyrrolizin-1-one.

3. A pharmaceutical composition comprising an effective amount of a compound and a pharmaceutically acceptable carrier, wherein the compound is of the formula:



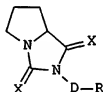
where

- each X independently is O, S, or NR₂;
R₂ is selected from the group consisting of cyano, nitro, hydrogen, C₁-C₄ alkyl, hydroxy, and C₁-C₄ alkoxy;
D is a direct bond or C₁-C₆ alkyl or alkenyl;
R is hydrogen, or an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring;
wherein R is optionally substituted with one substituent selected from the group consisting of hydrogen, halo, hydroxyl, nitro, trifluoromethyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, C₁-C₄ alkoxy, C₂-C₄ alkenyloxy, phenyl, phenoxy, benzyloxy, and amino;
or a pharmaceutically acceptable salt, ester, or solvate thereof.
4. The pharmaceutical composition of claim 3, further comprising an additional neurotrophic factor.
5. The pharmaceutical composition of claim 4, wherein the additional neurotrophic factor is selected from the group consisting of neurotrophic growth factor, brain derived growth factor, glial derived growth

- 81 -

factor, ciliary neurotrophic factor, insulin growth factor and active truncated derivatives thereof, acidic fibroblast growth factor, basic fibroblast growth factor, platelet-derived growth factors, neurotrophin-3, and neurotrophin-4/5.

6. A method of treating a neurological disorder in an animal, comprising:
administering to the animal an effective amount of a compound to stimulate growth of damaged peripheral nerves or to promote neuronal regeneration, wherein the compound is of the formula:



where

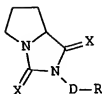
each X independently is O, S, or NR₂;
R₂ is selected from the group consisting of cyano, nitro, hydrogen, C₁-C₄ alkyl, hydroxy, and C₁-C₄ alkoxy;
D is a direct bond or C₁-C₄ alkyl or alkenyl;
R is hydrogen, or an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring;
wherein R is optionally substituted with one substituent selected from the group consisting of hydrogen, halo, hydroxyl, nitro, trifluoromethyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, C₁-C₄ alkoxy, C₂-C₄ alkenyloxy, phenyl, phenoxy, benzyloxy, and amino;
or a pharmaceutically acceptable salt, ester, or solvate thereof.

7. The method of claim 6, wherein the neurological disorder is selected from the group consisting of

- 82 -

- peripheral neuropathies caused by physical injury or disease state, physical damage to the brain, physical damage to the spinal cord, stroke associated with brain damage, and neurological disorders relating to neurodegeneration.
8. The method of claim 6, wherein the neurological disorder is selected from the group consisting of Alzheimer's Disease, Parkinson's Disease, amyotrophic lateral sclerosis, and Huntington's Disease.
9. The method of claim 6, wherein the neurological disorder is Alzheimer's Disease.
10. The method of claim 6, wherein the neurological disorder is Parkinson's Disease.
11. The method of claim 6, wherein the neurological disorder is amyotrophic lateral sclerosis.
12. The method of claim 6, wherein the neurological disorder is Huntington's Disease.
13. The method of claim 6, wherein the compound is non-immunosuppressive.
14. The method of claim 6, further comprising administering an additional neurotrophic factor.
15. The method of claim 14, wherein the additional neurotrophic factor is selected from the group consisting of neurotrophic growth factor, brain derived growth factor, glial derived growth factor, ciliary neurotrophic factor, insulin growth factor and active truncated derivatives thereof, acidic fibroblast growth factor, basic fibroblast growth factor, platelet-derived growth factors, neurotrophin-3, and neurotrophin-4/5.
16. A method of stimulating growth of damaged peripheral nerves, comprising:
administering to damaged peripheral nerves an effective amount of a compound to stimulate or promote growth of the damaged peripheral nerves, wherein the compound is of the formula:

- 83 -



where

each X independently is O, S, or NR₂;

5 R₂ is selected from the group consisting of
cyano, nitro, hydrogen, C₁-C₆ alkyl, hydroxy,
and C₁-C₆ alkoxy;

D is a direct bond or C₁-C₆ alkyl or alkenyl;

10 R is hydrogen, or an alicyclic or aromatic,
mono-, bi- or tricyclic, carbo- or
heterocyclic ring;

wherein R is optionally substituted with one
substituent selected from the group consisting of
hydrogen, halo, hydroxyl, nitro, trifluoromethyl,
C₁-C₆ straight or branched chain alkyl, C₂-C₆
15 straight or branched chain alkenyl, C₁-C₆ alkoxy, C₂-
C₆ alkenyloxy, phenyl, phenoxy, benzyloxy, and
amino;

or a pharmaceutically acceptable salt, ester, or solvate
thereof.

20 17. The method of claim 16, wherein the compound
is non-immunosuppressive.

18. The method of claim 16, further comprising
administrating an additional neurotrophic factor.

25 19. The method of claim 18, wherein the additional
neurotrophic factor is selected from the group
consisting of neurotrophic growth factor, brain derived
growth factor, glial derived growth factor, ciliary
neurotrophic factor, insulin growth factor and active
truncated derivatives thereof, acidic fibroblast growth
30 factor, basic fibroblast growth factor, platelet-derived
growth factors, neurotrophin-3, and neurotrophin-4/5.

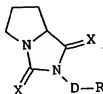
20. A method for promoting neuronal regeneration

- 84 -

and growth in animals, comprising:

administering to an animal an effective amount of a compound to promote neuronal regeneration, wherein the compound is of the formula:

5



where

each X independently is O, S, or NR₂;

R₂ is selected from the group consisting of cyano, nitro, hydrogen, C₁-C₄ alkyl, hydroxy, and C₁-C₄ alkoxy;

10

D is a direct bond or C₁-C₄ alkyl or alkenyl;

R is hydrogen, or an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring;

15

wherein R is optionally substituted with one substituent selected from the group consisting of hydrogen, halo, hydroxyl, nitro, trifluoromethyl, C₁-C₄ straight or branched chain alkyl, C₂-C₄ straight or branched chain alkenyl, C₁-C₄ alkoxy, C₂-C₄ alkenyloxy, phenyl, phenoxy, benzyloxy, and amino;

20

or a pharmaceutically acceptable salt, ester, or solvate thereof.

21. The method of claim 20, wherein the compound is non-immunosuppressive.

25

22. The method of claim 20, further comprising administering an additional neurotrophic factor.

23. The method of claim 22, wherein the additional neurotrophic factor is selected from the group consisting of neurotrophic growth factor, brain derived growth factor, glial derived growth factor, ciliary neurotrophic factor, insulin growth factor and active

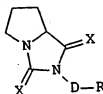
30

- 85 -

truncated derivatives thereof, acidic fibroblast growth factor, basic fibroblast growth factor, platelet-derived growth factors, neurotrophin-3, and neurotrophin-4/5.

24. A method for preventing neurodegeneration in
5 an animal, comprising:

administering to an animal an effective amount of a compound to prevent neurodegeneration, wherein the compound is of the formula:



10 where

each X independently is O, S, or NR_2 ;

R_2 is selected from the group consisting of cyano, nitro, hydrogen, $\text{C}_1\text{-C}_4$ alkyl, hydroxy, and $\text{C}_1\text{-C}_4$ alkoxy;

15 D is a direct bond or $\text{C}_1\text{-C}_6$ alkyl or alkenyl;

R is hydrogen, or an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring;

wherein R is optionally substituted with one
20 substituent selected from the group consisting of hydrogen, halo, hydroxyl, nitro, trifluoromethyl, $\text{C}_1\text{-C}_6$ straight or branched chain alkyl, $\text{C}_2\text{-C}_6$ straight or branched chain alkenyl, $\text{C}_1\text{-C}_4$ alkoxy, $\text{C}_2\text{-C}_4$ alkenyloxy, phenyl, phenoxy, benzyloxy, and
25 amino;

or a pharmaceutically acceptable salt, ester, or solvate thereof.

25. The method of claim 24, wherein the neurodegeneration is Alzheimer's Disease.

30 26. The method of claim 24, wherein the neurodegeneration is Parkinson's Disease.

27. The method of claim 24, wherein the

- 86 -

neurodegeneration is amyotrophic lateral sclerosis.

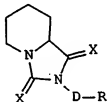
28. The method of claim 24, wherein the neurodegeneration is Huntington's Disease.

29. The method of claim 24, wherein the compound
5 is non-immunosuppressive.

30. The method of claim 24, further comprising administering an additional neurotrophic factor.

31. The method of claim 30, wherein the additional
neurotrophic factor is selected from the group
10 consisting of neurotrophic growth factor, brain derived growth factor, glial derived growth factor, ciliary neurotrophic factor, insulin growth factor and active truncated derivatives thereof, acidic fibroblast growth factor, basic fibroblast growth factor, platelet-derived
15 growth factors, neurotrophin-3, and neurotrophin-4/5.

32. A compound of the formula:



where

- each X independently is O, S, or NR₂;
- 20 R₂ is selected from the group consisting of cyano, nitro, hydrogen, C₁-C₄ alkyl, hydroxy, and C₁-C₄ alkoxy;
- D is a direct bond or a C₁-C₈ alkyl or alkenyl;
- 25 R is selected from the group consisting of hydrogen, phenyl, biphenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 1,2,3,4-tetrahydronaphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, indolyl, isoindolyl, indolinyl, benzofuranyl, benzothiophenyl,
30 indazolyl, benzimidazolyl, tetrahydrofuranlyl,

- 87 -

- 5 tetrahydropyranyl, pyridyl, pyrrolyl,
pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl,
quinolinyl; isoquinolinyl,
10 tetrahydroquinolinyl, quinoliziny, furyl,
thiophenyl, imidazolyl, oxazolyl,
benzopyranyl, thiazolyl, isotriazolyl,
oxadiazolyl, triazolyl, thiadiazolyl,
pyridazinyl, pyrimidinyl, pyrazinyl,
15 triazinyl, trithianyl, indoliziny, pyrazolyl,
pyrazolinyl, pyrazolidinyl, thienyl,
20 tetrahydroisoquinolinyl, cinnoliny, phthalazinyl,
quinazoliny, naphthyridinyl,
pteridinyl, carbazolyl, acridinyl, phenazinyl,
phenothiazinyl, phenoxazinyl, and adamantyl;
wherein R may be optionally substituted with one
substituent which is selected from the group
consisting of hydrogen, halo, hydroxyl, nitro,
trifluoromethyl; C₁-C₆ straight or branched chain
alkyl, C₂-C₆ straight or branched chain alkenyl, C₁-
20 C₄ alkoxy, C₂-C₄ alkenyloxy, phenyl, phenoxy,
benzyloxy, and amino;
or a pharmaceutically acceptable salt, ester, or solvate
thereof;
wherein when R is hydrogen, D is a C₃-C₆ alkyl or
25 alkenyl;
wherein when R is phenyl and D is a bond, R must be
substituted with C₂-C₃ or C₃-C₆ straight or branched chain
alkyl or alkenyl, C₃-C₄ alkoxy or C₂-C₄ alkenyloxy,
phenyl, phenoxy, benzyloxy, or amino.
30 33. The compound according to claim 32 that is
selected from the group consisting of:
2-Benzyl-2,5,6,7,8,8a-hexahydro-2-azaindolizine-
1,3-dione,
2-Benzyl-3-thioxo-2,5,6,7,8,8a-hexahydro-2-
35 azaindolizin-1-one,

- 88 -

2-(2-phenylethyl)-3-thioxo-2,5,6,7,8,8a-hexahydro-
2-azaindolizine-1-one,

2-Heptyl-2,5,6,7,8,8a-hexahydro-2-azaindolizine-
1,3-dione,

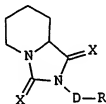
5 2-Octyl-2,5,6,7,8,8a-hexahydro-2-azaindolizine-1,3-
dione,

2-(3-phenylpropyl)-3-thioxo-2,5,6,7,8,8a-hexahydro-
2-azaindolizine-1-one,

2-hexyl-2,5,6,7,8,8a-hexahydro-2-azaindolizine-1,3-
10 dione, and

2-Cyclohexyl-2,5,6,7,8,8a-hexahydro-2-
azaindolizine-1,3-dione.

34. A pharmaceutical composition comprising an
effective amount of a compound and a pharmaceutically
15 acceptable carrier, wherein the compound is of the
formula:



where

each X independently is O, S, or NR₂;

20 R₂ is selected from the group consisting of
cyano, nitro, hydrogen, C₁-C₆ alkyl, hydroxy,
and C₁-C₆ alkoxy;

D is a direct bond or C₁-C₆ alkyl or alkenyl;

R is hydrogen, or an alicyclic or aromatic,
25 mono-, bi- or tricyclic, carbo- or
heterocyclic ring;

wherein R is optionally substituted with one
substituent selected from the group consisting of
hydrogen, halo, hydroxyl, nitro, trifluoromethyl,

30 C₁-C₆ straight or branched chain alkyl, C₂-C₆
straight or branched chain alkenyl, C₁-C₆ alkoxy, C₂-

- 89 -

C₄ alkenyloxy, phenyl, phenoxy, benzyloxy, and amino;

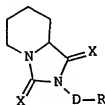
or a pharmaceutically acceptable salt, ester, or solvate thereof.

- 5 35. The pharmaceutical composition of claim 34, further comprising an additional neurotrophic factor.

36. The pharmaceutical composition of claim 35, wherein the additional neurotrophic factor is selected from the group consisting of neurotrophic growth factor,
10 brain derived growth factor, glial derived growth factor, ciliary neurotrophic factor, insulin growth factor and active truncated derivatives thereof, acidic fibroblast growth factor, basic fibroblast growth factor, platelet-derived growth factors, neurotrophin-3,
15 and neurotrophin-4/5.

37. A method of treating a neurological disorder in an animal, comprising:

- administering to the animal an effective amount of a compound to stimulate growth of damaged peripheral
20 nerves or to promote neuronal regeneration, wherein the compound is of the formula:



where

- each X independently is O, S, or NR₂;
25 R₂ is selected from the group consisting of cyano, nitro, hydrogen, C₁-C₄ alkyl, hydroxy, and C₁-C₄ alkoxy;
D is a direct bond or C₁-C₄ alkyl or alkenyl;
R is hydrogen, or an alicyclic or aromatic,
30 mono-, bi- or tricyclic, carbo- or heterocyclic ring;

- 90 -

wherein R is optionally substituted with one substituent selected from the group consisting of hydrogen, halo, hydroxyl, nitro, trifluoromethyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, C₁-C₄ alkoxy, C₂-C₄ alkenyloxy, phenyl, phenoxy, benzyloxy, and amino;

or a pharmaceutically acceptable salt, ester, or solvate thereof.

38. The method of claim 37, wherein the neurological disorder is selected from the group consisting of peripheral neuropathies caused by physical injury or disease state, physical damage to the brain, physical damage to the spinal cord, stroke associated with brain damage, and neurological disorders relating to neurodegeneration.

39. The method of claim 37, wherein the neurological disorder is selected from the group consisting of Alzheimer's Disease, Parkinson's Disease, amyotrophic lateral sclerosis, and Huntington's Disease.

40. The method of claim 37, wherein the neurological disorder is Alzheimer's Disease.

41. The method of claim 37, wherein the neurological disorder is Parkinson's Disease.

42. The method of claim 37, wherein the neurological disorder is amyotrophic lateral sclerosis.

43. The method of claim 37, wherein the neurological disorder is Huntington's Disease.

44. The method of claim 37, wherein the compound is non-immunosuppressive.

45. The method of claim 37, further comprising administering an additional neurotrophic factor.

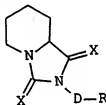
46. The method of claim 45, wherein the additional neurotrophic factor is selected from the group consisting of neurotrophic growth factor, brain derived

- 91 -

growth factor, glial derived growth factor, ciliary neurotrophic factor, insulin growth factor and active truncated derivatives thereof, acidic fibroblast growth factor, basic fibroblast growth factor, platelet-derived growth factors, neurotrophin-3, and neurotrophin-4/5.

47. A method of stimulating growth of damaged peripheral nerves, comprising:

administering to damaged peripheral nerves an effective amount of a compound to stimulate or promote growth of the damaged peripheral nerves, wherein the compound is of the formula:



where

- each X independently is O, S, or NR_2 ;
 R_2 is selected from the group consisting of cyano, nitro, hydrogen, $\text{C}_1\text{-C}_4$ alkyl, hydroxy, and $\text{C}_1\text{-C}_4$ alkoxy;
 D is a direct bond or $\text{C}_1\text{-C}_6$ alkyl or alkenyl;
 R is hydrogen, or an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring;
 wherein R is optionally substituted with one substituent selected from the group consisting of hydrogen, halo, hydroxyl, nitro, trifluoromethyl, $\text{C}_1\text{-C}_6$ straight or branched chain alkyl, $\text{C}_2\text{-C}_6$ straight or branched chain alkenyl, $\text{C}_1\text{-C}_4$ alkoxy, $\text{C}_2\text{-C}_4$ alkenyloxy, phenyl, phenoxy, benzyloxy, and amino;
 or a pharmaceutically acceptable salt, ester, or solvate thereof.

48. The method of claim 47, wherein the compound

- 92 -

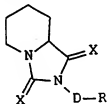
is non-immunosuppressive.

49. The method of claim 47, further comprising administering an additional neurotrophic factor.

50. The method of claim 49, wherein the additional
 5 neurotrophic factor is selected from the group
 consisting of neurotrophic growth factor, brain derived
 growth factor, glial derived growth factor, ciliary
 neurotrophic factor, insulin growth factor and active
 truncated derivatives thereof, acidic fibroblast growth
 10 factor, basic fibroblast growth factor, platelet-derived
 growth factors, neurotrophin-3, and neurotrophin-4/5.

51. A method for promoting neuronal regeneration
 and growth in animals, comprising:

administering to an animal an effective amount of a
 15 compound to promote neuronal regeneration, wherein the
 compound is of the formula:



where

- each X independently is O, S, or NR₂;
- 20 R₂ is selected from the group consisting of
 cyano, nitro, hydrogen, C₁-C₆ alkyl, hydroxy,
 and C₁-C₆ alkoxy;
- D is a direct bond or C₁-C₆ alkyl or alkenyl;
- R is hydrogen, or an alicyclic or aromatic,
 25 mono-, bi- or tricyclic, carbo- or
 heterocyclic ring;
- wherein R is optionally substituted with one
 substituent selected from the group consisting of
 hydrogen, halo, hydroxyl, nitro, trifluoromethyl,
 30 C₁-C₆ straight or branched chain alkyl, C₂-C₆
 straight or branched chain alkenyl, C₁-C₆ alkoxy, C₂-

- 93 -

C₄ alkenyloxy, phenyl, phenoxy, benzyloxy, and amino;

or a pharmaceutically acceptable salt, ester, or solvate thereof.

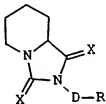
5 52. The method of claim 51, wherein the compound is non-immunosuppressive.

53. The method of claim 51, further comprising administering an additional neurotrophic factor.

54. The method of claim 53, wherein the additional
10 neurotrophic factor is selected from the group consisting of neurotrophic growth factor, brain derived growth factor, glial derived growth factor, ciliary neurotrophic factor, insulin growth factor and active truncated derivatives thereof, acidic fibroblast growth
15 factor, basic fibroblast growth factor, platelet-derived growth factors, neurotrophin-3, and neurotrophin-4/5.

55. A method for preventing neurodegeneration in an animal, comprising:

20 administering to an animal an effective amount of a compound to prevent neurodegeneration, wherein the compound is of the formula:



where

- 25 each X independently is O, S, or NR₂;
R₂ is selected from the group consisting of cyano, nitro, hydrogen, C₁-C₄ alkyl, hydroxy, and C₁-C₄ alkoxy;
D is a direct bond or C₁-C₃ alkyl or alkenyl;
R is hydrogen, or an alicyclic or aromatic,
30 mono-, bi- or tricyclic, carbo- or heterocyclic ring;

- 94 -

- wherein R is optionally substituted with one substituent selected from the group consisting of hydrogen, halo, hydroxyl, nitro, trifluoromethyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, C₁-C₆ alkoxy, C₂-C₆ alkenyloxy, phenyl, phenoxy, benzyloxy, and amino;
- or a pharmaceutically acceptable salt, ester, or solvate thereof.
56. The method of claim 55, wherein the neurodegeneration is Alzheimer's Disease.
57. The method of claim 55, wherein the neurodegeneration is Parkinson's Disease.
58. The method of claim 55, wherein the neurodegeneration is amyotrophic lateral sclerosis.
59. The method of claim 55, wherein the neurodegeneration is Huntington's Disease.
60. The method of claim 55, wherein the compound is non-immunosuppressive.
61. The method of claim 55, further comprising administering an additional neurotrophic factor.
62. The method of claim 61, wherein the additional neurotrophic factor is selected from the group consisting of neurotrophic growth factor, brain derived growth factor, glial derived growth factor, ciliary neurotrophic factor, insulin growth factor and active truncated derivatives thereof, acidic fibroblast growth factor, basic fibroblast growth factor, platelet-derived growth factors, neurotrophin-3, and neurotrophin-4/5.

INTERNATIONAL SEARCH REPORT

 Intern. Application No.
 PCT/US 00/30436

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D487/04 A61K31/435 A61K31/415 A61P25/28 A61P27/00 A61P17/14	
According to International Patent Classification (IPC) or to both national classification and IPC	
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07D	
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched	
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, PAJ, CHEM ABS Data	
C. DOCUMENTS CONSIDERED TO BE RELEVANT	
Category*	Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No.
X	Z-K-LIAO ET. AL.: "Synthesis of Substituted 2-Imidazolidinones and Annelated Hydantoinis vis Amidoalkylation Transformations" JOURNAL OF ORGANIC CHEMISTRY, vol. 49, no. 25, 14 December 1984 (1984-12-14), pages 4745-52, XP000973133 page 4746, compound no. 12
X	DATABASE WPI Week 7734 Derwent Publications Ltd., London, GB; AN 1977-60444Y XP002157415 & JP 52 083686 A (MITSUBISHI CHEM. IND. LTD.), 12 July 1977 (1977-07-12) claims; examples
-/-	
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.	
<input checked="" type="checkbox"/> Patent family members are listed in annex.	
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another claim or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "Z" document member of the same patent family	
Date of the actual completion of the international search 16 January 2001	Date of mailing of the international search report 30. 01. 01
Name and mailing address of the ISA European Patent Office, P.B. 5618 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Helps, I

INTERNATIONAL SEARCH REPORT

 Internat'l Application No
 PCT/US 00/30436

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Week 199303 Derwent Publications Ltd., London, GB; AN 1993024093 XP002157416 & JP 04 352784 A (SANKYO), 7 December 1992 (1992-12-07) page 31 -page 33	32
A	L. CAPUNO ET. AL.: "Neue Hydantoine mit Brückenkopf-Stickstoff bzw. Spiran-Struktur." CHEMISCHE BERICHTE, vol. 103, 1970, pages 2394-2402, XP000882488 page 2396, compound no. 7a, 7b, 9a, 9b	1
A	J.J.M. SLEECKX ET. AL.: "Proton Magnetic Resonance Study of the conformation of the Pyrrolidine Ring in Some Proline Thiohydantoins." COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS , vol. 53, 1988, pages 2503-10, XP000973132 page 2507, compounds 1a-1d	1
A	US 4 230 709 A (JAMIESON ET. AL.) 28 October 1980 (1980-10-28) claims; example 8	1,32
A	US 5 232 936 A (MOCHIDA ET. AL.) 3 August 1993 (1993-08-03) claims; examples	1-62
A	WO 88 05653 A (PROCTOR ET. AL.) 11 August 1988 (1988-08-11) claims 1,13; examples	1-62
A	US 5 145 862 A (AIZENMAN ET. AL.) 8 September 1992 (1992-09-08) column 3, line 33 -column 4, line 61; claims; examples	1-62

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/30436

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 6 - 31 and 37 - 62 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat'l Application No

PCT/US 00/30436

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 52083686 A	12-07-1977	JP 1258349 C JP 59033593 B	29-03-1985 16-08-1984
JP 04352784 A	07-12-1992	NONE	
US 4230709 A	28-10-1980	GB 1600880 A	21-10-1981
US 5232936 A	03-08-1993	JP 1061465 A JP 2764262 B US RE35279 E AT 147073 T AU 646967 B AU 2122592 A AU 623676 B AU 4064789 A CA 1338866 A DE 68927599 D DE 68927599 T DK 100190 A EP 0355827 A ES 2098222 T GR 3022223 T WO 9002126 A JP 1893406 C JP 4128266 A JP 6015539 B NO 176478 B US 5004751 A US 5202339 A AT 78815 T AU 609180 B AU 2157788 A CA 1312083 A DE 3873225 A DE 3873225 T DK 207389 A EP 0305947 A ES 2042666 T FI 891933 A, B, GR 3005392 T WO 8901934 A NO 891689 A, B, US 4914099 A	08-03-1989 11-06-1998 18-06-1996 15-01-1997 10-03-1994 15-10-1992 21-05-1992 23-03-1990 21-01-1997 13-02-1997 15-05-1997 14-06-1990 28-02-1990 01-05-1997 30-04-1997 08-03-1990 26-12-1994 28-04-1992 02-03-1994 02-01-1995 02-04-1991 13-04-1993 15-08-1992 26-04-1991 02-03-1989 29-12-1992 03-09-1992 28-01-1993 28-04-1989 08-03-1989 16-12-1993 24-04-1989 24-05-1993 09-03-1989 24-04-1989 03-04-1990
WO 8805653 A	11-08-1988	AU 1362488 A US 5352442 A US 5472687 A US 5470876 A US 5714482 A US 5716947 A US 5714510 A US 5723502 A US 5728714 A US 6150405 A	24-08-1988 04-10-1994 05-12-1995 28-11-1995 03-02-1998 10-02-1998 03-02-1998 03-03-1998 17-03-1998 21-11-2000
US 5145862 A	08-09-1992	US 5091391 A	25-02-1992

THIS PAGE BLANK (USPTO)